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RENAL REGULATION OF THE EXTRACELLULAR FLUID: I. A STUDY OF HOMŒOSTASIS IN A PATIENT WITH A DUODENAL FISTULA.

By D. A. DENTON,

The Royal Melbourne Hospital, Melbourne.

IN 1878, Claude Bernard made his famous induction as to the equilibrium state in the tissue fluids. Researches since then have shown the extent to which enzyme reactions, inherent to the processes of life, are varied by their ionic environment. It has become increasingly apparent that the maintenance of the stable state within the tissue fluids under circumstance of disease is a basic problem of medical practice.

The kidney controls homœostasis of the non-volatile substances in the extracellular fluid. It may vary excretion of either solutes or the solvent. Two mechanisms are described:

1. Regulation, to a constant level, of the concentration of several electrolytes and non-electrolytes (the word "constant" here implies "limited range of variability"). That is, "renal thresholds" exist for these substances. The kidney excretes the substance when the plasma level rises above normal, and ceases to excrete it when the plasma level falls below normal.

2. Regulation of the osmotic pressure of the extracellular fluid so as to maintain isotonicity with intracellular fluid. If the concentration of electrolytes in the extracellular fluid falls, the kidney excretes water in order to maintain the osmotic pressure constant.

This is an account of a patient, aged seventeen years, who developed a duodenal fistula. The fistula fluid contained twice as much Na^+ as Cl^-. The loss of two to four litres of this fluid daily would obviously tend to lower the level of Na^+ in the extracellular fluid at a greater rate than the Cl^-. However, the ratio of these ions in the extracellular fluid remained approximately constant. The explanation appeared simple. The kidney maintained this homœostasis by excreting a sufficient excess of Cl^- relative to Na^+. The very interesting feature was that the kidney did this despite the fact that the level of Cl^- in the plasma was constantly depleted below the "renal threshold" for Cl^-.

The proposition will be made in this and subsequent papers that a post-gastrectomy type of duodenal fistula (Figure I) represents an experimental technique for studying the renal regulation of electrolytes, when twice as much Na^+ as Cl^- is subtracted from the body. An important feature of this technique is that there is a functioning gastro-jejunostomy, and hence free absorption of water and food from the intestines is possible. Thus, it is possible to study electrolyte subtraction in the absence of effects due to primary dehydration (Marriott, 1947) or starvation. The renal mechanism regulating extracellular homœostasis is therefore presented with two conflicting problems.

1. *Regulation of Osmotic Pressure.*—The fluid lost from the fistula is isotonic. Because of a functioning gastro-jejunostomy there is free intake and absorption of water from the intestine. A fall in extracellular osmotic pressure will occur if this set of conditions continues without compensation. If the kidney is to maintain a normal extracellular osmotic pressure, it will have to excrete water and retain electrolytes (Verney, 1946). In doing this, it may reduce the total volume of the extracellular fluid (Kerfel-Fronius, 1935; Darrow and Yannet, 1936; McCance, 1938; Nadal, Pedersen and Maddock, 1941). Marriott (1947) has termed this reduction of extracellular volume "secondary dehydration".

2. *Regulation of Extracellular Ionic Pattern.*—The fluid lost contains twice as much Na^+ as Cl^- (Figure II)—that is, Na^+ is lost from the extracellular fluid at twice the rate of Cl^-. Therefore the level of Na^+ in the extracellular fluid will fall at twice the rate of the level of Cl^-. This represents a profound strain on the pH control of the extracellular fluid. Moreover, there is no biologically inactive cation which can play a role analogous to that of the bicarbonate anion, such as occurs when Cl^- is subtracted from the extracellular fluid in excess of Na^+—for example, pyloric stenosis, gastric fistula. If a large rise of hydrogen ion concentration is to be avoided, the kidney will have to excrete the anion Cl^- in excess of Na^+.

It will be shown in this and subsequent papers that when Na^+ is subtracted from the body in excess of Cl^-, the ratio $\frac{Cl}{Na}$ in the extracellular fluid remains invariant relative to the size of the distorting stress. This is because the kidney excretes a sufficient excess of Cl^- relative to Na^+. This renal mechanism operates independently of the fact that the extracellular level of Cl^- may be reduced much below the "renal threshold" for Cl^-. It also appears to operate even when there is a severe stress on the extracellular osmoregulation causing secondary dehydration.

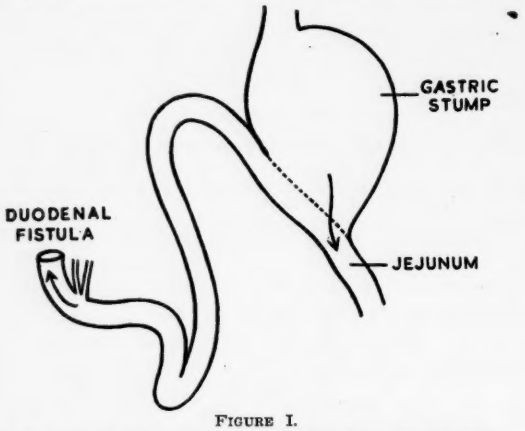


FIGURE I.

Diagram showing a post-gastrectomy type of duodenal fistula.

Two problems arise: (i) If the kidney did not behave in this manner, the probable result would be a greater degree of acidæmia than is observed. Therefore the first question is: "What specific cause acts at the renal level to determine a large Cl excretion despite a plasma level below the 'renal threshold'?"

(ii) Marriott (1947), in his Croonian Lectures, suggested that the quantity of chloride in the urine (Fantus test, 1936) could be used as a diagnostic criterion of the presence or absence of chloride depletion in the extracellular fluid. However, as will be shown in this patient, the relation between plasma and urinary chloride is not simple and direct. Evidence will be cited to suggest that Marriott's views require modification in that group of cases in which Na^+ is lost from the body in excess of Cl^-.

Clinical Observations.

The boy developed the duodenal fistula after a partial gastrectomy performed because of a persistently bleeding duodenal ulcer. He lost up to the equivalent of one quarter of his extracellular fluid daily, and during his illness was given approximately 26 gallons of fluid intravenously.

The clinical history,[1] in brief, is as follows.

Two years before his admission to hospital, the patient had had a gangrenous appendix removed. Two months after this, a collection of pus was drained from Morrison's pouch. For twelve months he had become increasingly fatigued, and when admitted to hospital had a hæmoglobin value of 37%. One week after admission, subsequent to blood transfusion, a large penetrating ulcer, one inch in diameter, was oversewn in the duodenum, and a grossly fibrotic gall-bladder to which it was adherent was removed. After the operation vomiting occurred, and large amounts of fluid were aspirated from the stomach. Biochemically, the findings were similar to those of Nadal, Pedersen and Maddock (1941), Marriott (1947) and numerous other observers, namely, a rise in hæmatocrit and plasma specific gravity readings, associated with diminution of plasma chloride and the presence of only very small quantities of chloride in the urine. During the following twenty-five days the patient had several further hæmorrhages, as shown by melena. In view of the failure of conservative treatment to control the hæmorrhage, partial gastrectomy with gastro-jejunostomy was performed. Five days after operation the duodenal suture line parted, and the patient developed a rapidly spreading general peritonitis. Under general anæsthesia, the abdomen was drained.

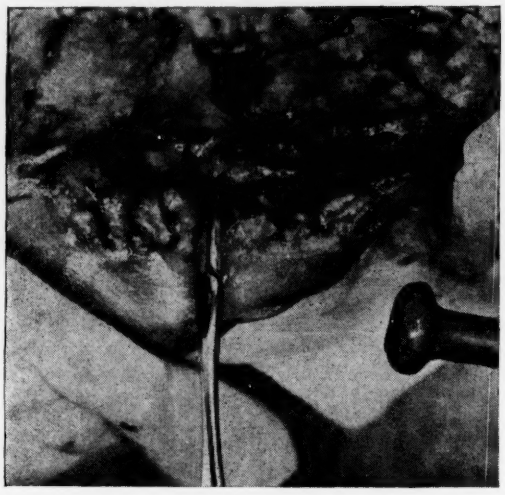


FIGURE IA.

Day 43. The forceps indicate the duodenal fistula. After the patient took milk fluids orally, a peristaltic wave started in the gastric stump, and passed down the efferent loop of the gastro-jejunostomy. Within thirty seconds there was an increased flow from the fistula (compare I. P. Pavlov, Lecture VIII, 1897). A possible explanation of the relation between the volume of fistula flow and intravenous ionic intake (Graphs II and III) is that the latter determined the state of the peripheral circulation. Subsequent investigations have shown that the apparent failure of the processes of healing in this patient was most probably associated with the major disturbances of intermediary metabolism which have been observed to occur in gross potassium depletion. It was also noted during the last 10 to 15 days of life that the incisions made for intravenous infusion did not heal.

Copious drainage persisted from the right paramedian incision, the edges of which became digested. Through the fistula thus established up to four litres of mixed duodenal, pancreatic, and biliary secretion were lost from the body each day. The fistula flow was collected by suction of an electric pump. During the forty-five days that the fistula drained, the patient also had persistent diarrhœa. The two probable causes of this were intestinal adhesions, and the absence of pancreatic secretions from the intestine. Diarrhœa would also represent a loss of Na^+ in excess of Cl^- from the body. However, this was a minor factor compared with the loss from the fistula.

On the thirty-sixth day after establishment of the fistula, surgical closure was attempted, and entero-enterostomy was performed. That night bile was aspirated from the "stomach stump", but one day later copious drainage was recommenced through the wound. Over the next three days, the abdominal wall between the costal margins and the umbilicus sloughed, exposing the upper abdominal viscera. No further transfusion was given, and the patient's clinical condition

[1] This is not intended to be an adequate account of the many clinical problems which influenced the surgeons and consulting physicians in their management of this patient.

gradually deteriorated until just prior to death on the forty-fifth day the cardiac rate was approaching 170 per minute, the blood pressure was unregisterable, and the respirations were of greater than normal amplitude at the rate of 40 per minute. The pupillary reflexes were extraordinarily hyper-excitable to light stimulus, responding with alternate maximum dilatation and contraction to the mere passage of a shadow across one eye.

At autopsy, the positive findings were that the coils of small and large bowel were matted in an extensive plastic peritonitis, and that the duodenal stump was widely patent. The kidneys and suprarenals were normal.

Biochemical Observations.

The accompanying graphs I to VI on a common time axis record the biochemical observations over the forty-five-day period during which the patient remained alive after the development of the fistula.

For purposes of simple comparison and physiological accuracy (Gamble, 1947), the biochemical readings are expressed in milliequivalents per litre. The normal plasma values are:

Cations

Na^+	= 142	milliequivalents	per litre
K^+	= 5	,,	,, ,,
Ca^{++}	= 5	,,	,, ,,
Ma^{++}	= 3	,,	,, ,,
	155		

Anions

HCO_3^-	= 27	milliequivalents	per litre
Cl^-	= 103	,,	,, ,,
HPO_4	= 2	,,	,, ,,
SO_4	= 1	,,	,, ,,
Organic acid	= 6	,,	,, ,,
Protein	= 16	,,	,, ,,
	155		

Because of the necessity of electrical neutrality, there are an equivalent number of anions and cations. Conversion to milliequivalents per litre is made by dividing milligrammes per litre by atomic weight and multiplying by the valency. Conversion of the bicarbonate to milliequivalents per litre is made by dividing volumes *per centum* of CO_2 by 2·22. The base equivalence of protein

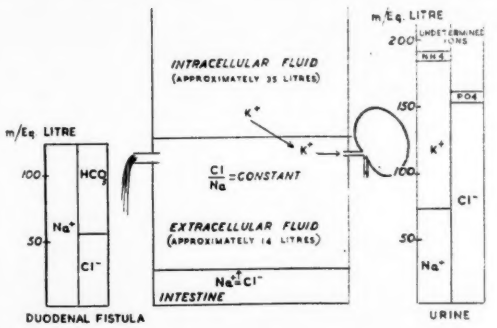


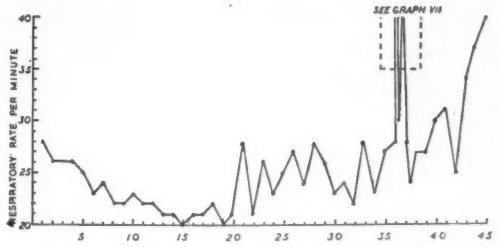
FIGURE II.

Analyses on day 40 showing the renal response to the subtraction of twice as much Na^+ as Cl^- from the body. This ratio mechanism appeared to operate despite the stress on the extracellular osmotic pressure, and independent of the "renal threshold" for Cl^-. At the times it was studied, Na^+ and Cl^- ions were either absent from the intake or were present in equivalent quantities. For this reason, precise details of the intravenous and oral ionic intake have not been recorded.

as milliequivalents per litre is obtained by multiplying grammes of protein per 100 millilitres by the Van Slyke factor, 2·43. The physiological fallacy of expressing Cl^- determinations as NaCl was pointed out by Cushny in 1917. Because of this, it is better to regard each drop of silver nitrate used in the simple Fantus test as representing approximately 20 milliequivalents per litre of chloride ion, rather than 1·0 gramme of NaCl.

The chemical composition of the fistula fluid was 121 milliequivalents of Na^+ and 54 milliequivalents per litre of Cl^-. The excess Na^+ was present with the anion HCO_3^- (Figure II). Positive results to tests for trypsin and bile salts were obtained. The fact that the Na^+ content was low relative to normal extracellular concentration possibly reflects the fact that the extracellular Na^+ content was low at the time these specimens of fistula fluid were collected for analysis (compare Ball, 1930, and Johnston and Ball, 1930).

A full series of graphs has been shown, but it is particularly desired to direct attention on two episodes in the history.



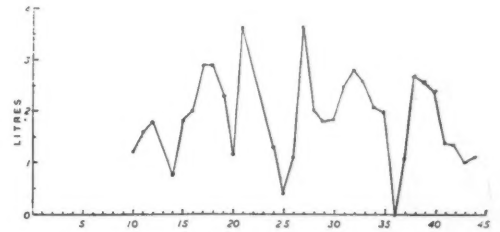
GRAPH I.

Daily average of the respiratory rate per minute. (Note the relative instability after the twentieth day.)

A. Over the period from the eighteenth to the twenty-first day ionic replacement therapy was withheld, this being in accordance with the belief that a large chloride content of the urine denoted the absence of ionic depletion in the extracellular fluid. (Marriott, 1947.) The following interesting observations were made.

The patient's general condition deteriorated until on the morning of the twenty-first day it was observed that:

1. The blood pressure which had gradually fallen from a normal of 150 millimetres of mercury systolic was now 85 to 95 millimetres of mercury systolic with 10 millimetres of mercury of *pulsus alternans*, and the cardiac rate was 130 per minute.
2. The pulse was practically impalpable, and in the cold cyanotic extremities, the capillary return was very poor.
3. The patient's temperature was 97·2° F.
4. The patient was mentally confused, and complained of great weakness and cramps in his toes.



GRAPH II.

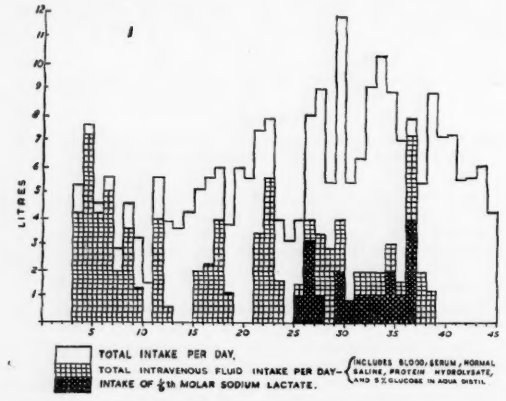
Flow from the fistula per day. (Surgical closure on day 36.)

5. The fistula output in the preceding twenty-four hours had been only one litre, despite an oral intake of twelve litres of fluid in the preceding forty-eight hours.
6. The respiratory rate had risen to 28 per minute and was of greater than normal amplitude.
7. The veins were collapsed.
8. The plasma chloride content was 57 milliequivalents per litre.

Thus, the condition of the patient was one of peripheral circulatory failure.

Nadal, Pedersen and Maddock (1941) and Marriott (1947) stated that diminished extracellular osmotic pressure, consequent on abnormal electrolyte loss, caused a circulatory failure. The above facts, *plus* the response to intravenously administered normal saline to be recounted, probably indicate a cause and effect relation in this case. The important feature of this episode is the

urinary chloride curve. The urinary chloride readings by the ward Fantus tests had remained of the order of magnitude of the line joining the laboratory readings of the fourth and seventeenth days (graph V). Now on the nineteenth day, despite the fact that there had been a large fistula loss, along with no intravenous administration of NaCl for thirty-six hours, and therefore probably a falling plasma chloride concentration, the urinary chloride content rose to a maximum of 154 milliequivalents per litre. It then fell to a minimum of 43 milliequivalents per litre on the morning of the twenty-first day, at which stage, as indicated, the plasma chloride content was 57 milliequivalents per litre. Intravenous administration of 5% glucose in normal saline was commenced. After twenty-four hours, during which the patient had six litres of saline, the systolic blood pressure had risen to 145 millimetres of mercury and the respiratory rate had fallen to 20 per minute.


LITRES
TOTAL INTAKE PER DAY.
TOTAL INTRAVENOUS FLUID INTAKE PER DAY—INTAKE OF 1/6th MOLAR SODIUM LACTATE.
INCLUDES BLOOD, SERUM, NORMAL SALINE, PROTEIN HYDROLYSATE, AND 5% GLUCOSE IN AQUA DISTIL

GRAPH III.

Fluid intake chart. (A relation is suggested between intravenous ionic intake and fistula flow—Graph II.)

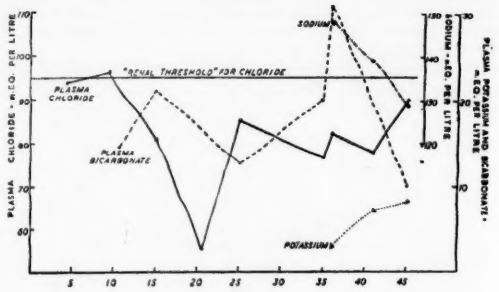
B. On the thirty-sixth day surgical closure of the fistula was attempted. Pre-operative medication, "Omnopon" 1/6th grain and hyoscine 1/200th grain, was followed by "Pentothal" (1·5 grammes), nitrous oxide, and oxygen anæsthesia. Probably the summated effect of these drugs was to depress the respiratory centre. Hence there was suppression for some time of a major factor regulating the blood pH. This precipitated some extremely interesting events.

On his return to the ward, the respiratory rate of the unconscious patient rose rapidly to 60 per minute. There was no evidence of a cardiac or pulmonary cause. Hence rapid intravenous administration of 1/6th molar sodium lactate solution was instituted. Graph VII records the relation between respiratory rate and the intravenous sodium lactate content over the following forty-six hours. It can be seen that in the first one and a half hours, 1·5 litres of sodium lactate (250 milliequivalents of Na^+) lowered the respiratory rate to 36 per minute—and a further litre (160 milliequivalents of Na^-) at the fourth hour caused a fall to 30 per minute. At the sixth hour sodium lactate administration was recommenced, and the respiratory rate gradually began to rise until at the tenth hour it had reached 40 per minute. The rate of sodium lactate administration was doubled, and at the twelfth hour, the respiratory rate was 48 per minute. At this point, for the first time since the fistula developed, the urine reaction changed from maximum acidity to the order of maximum alkalinity (pH 8·0), and Fantus test showed the urinary chloride content to be less than 20 milliequivalents per litre. Sodium lactate administration was stopped. The respiratory rate dropped gradually over the following thirty-four hours, the curve being of an exponential form. Blood analysis at this time revealed the plasma bicarbonate content to be raised, the sodium content to be normal, and the plasma chloride content to be 83 milliequivalents per litre, with a urinary chloride value of less than 20 milliequivalents per litre. That is, the 650 milliequivalents of sodium ion which had been given in the preceding twenty-four hours had restored the extracellular sodium to normal and, coincident with this, the chloride excretion had ceased.

Discussion.

The Duodenal Fistula.

Early investigations of blood changes in duodenal fistula were made on dogs by Walters, Waltman and Bollman of the Mayo Foundation in 1926. In those fistulæ with gastro-jejunostomy, they noted an increased chloride loss from the urinary and intestinal tracts, but attributed this to "a disturbance in motility of the upper intestinal tract". Kittleson (1933), and Bartlett and Lowell (1938) have reviewed the surgical aspects of 106 cases dating since 1865, but no biochemical studies on man appear to have been reported.


PLASMA CHLORIDE — M.EQ. PER LITRE
"RENAL THRESHOLD" FOR CHLORIDE
PLASMA CHLORIDE
PLASMA BICARBONATE
SODIUM
POTASSIUM
PLASMA BICARBONATE — VOLS. PER CENT. CO2 CAPACITY
PLASMA SODIUM AND POTASSIUM — M.EQ. PER LITRE

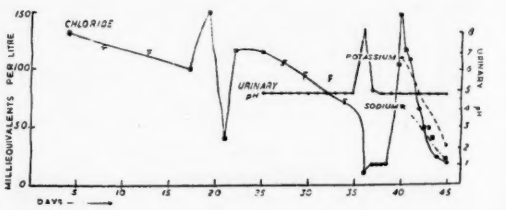
GRAPH IV.

Plasma biochemistry—chloride, sodium, potassium, and bicarbonate ("alkali reserve")—all expressed as milliequivalents per litre of plasma. The "renal threshold" drawn is that determined by Aitken (1929).

The Extracellular Fluid.

The question as to the exact mechanism by which the kidney regulates the concentration of an extracellular electrolyte is of great clinical, as well as physiological, importance. This is because it is widespread practice to assess a patient's need of ionic replacement therapy on the belief that the kidney excretes an ion when it is in excess and ceases to excrete it when the body stores are depleted.

Thus, Marriott (1947) in his Croonian Lectures, described the clinical and pathological features of pure salt depletion as seen, in uncomplicated form, in individuals whose salt loss arises from sweating due to heat. He



GRAPH V.

Urine analyses—chloride, sodium, potassium and pH. Expressed as milliequivalents per litre. (F indicates the order of magnitude of the results of the ward Fantus tests for Cl^-.)

emphasized the fact that the same clinical and pathological features are frequently to be seen in medical and surgical wards in cases of vomiting, gastric or intestinal suction drainage, biliary or intestinal fistula, diarrhœa, and Addison's disease.

He stated that the kidneys practically stop secreting salt as soon as the plasma level falls below normal—that is, sodium 139 to 152 milliequivalents per litre, chloride 97 to 110 milliequivalents per litre,[1] with the

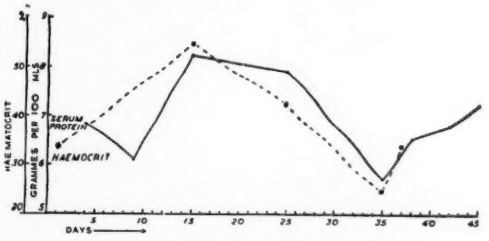
[1] Aitken (1929) found the nearest approximation to a renal threshold for chloride in man to be in the neighbourhood of 95 to 100 milliequivalents per litre of plasma. Rehberg (1926) found the renal threshold for chloride in man to be 106 milliequivalents per litre of plasma.

exception of Addison's disease in which excretion may continue even when plasma chloride is below 85 milliequivalents per litre (Anderson and Lyall, 1937). He stated the main function of Na and Cl ions appeared to be to supply osmotic pressure so that isotonicity with intracellular fluid is preserved, but in so far as 90% of the total base of the extracellular fluid is represented by sodium, and 70% of the acid by chloride, they play principal parts in the maintenance of acid-base balance.

He held that

> serious depletion of Sodium and Chloride gives rise to the following conditions: (*a*) An invariable loss of total osmotic pressure of extracellular fluid. In consequence the kidneys excrete water and there is diminution of extracellular fluid volume—extracellular or secondary dehydration. (*b*) A possible disturbance of acid-base equilibrium if loss of chloride and sodium ions is not proportionate. Both changes produce clinical effects, but I would submit that the former is more important. The only effect which seems mainly or wholly attributable to alkalosis or acidosis, when caused by vomiting or diarrhœa, is perhaps some difference of little practical significance in the character of the breathing.

From a diagnostic point of view he accorded "the absence of chloride from the urine a place of first importance", and quoted ten cases of undiagnosed marked salt depletion due to a variety of surgical causes he recently observed, in all of which chloride was absent from the urine.



GRAPH VI.

Hæmatocrit and total proteins of serum—suggests hæmoconcentration at times when peripheral circulatory failure occurred. The patient did not at any time become œdematous.

The possible error in considering renal tubular behaviour towards extracellular electrolytes in terms of the word "salt" was pointed out by Cushny (1917). Homer Smith (1937) pointed out that

> In view of the nature of strong electrolytes, it is incorrect to treat any pair of ions, such as Na^+ and Cl^-, as though they existed in the plasma in the form of a molecule. Yet because these are the predominant ions in both plasma and urine and because Cl^- always carries an equivalent quantity of cation mostly Na^+, while Na^+ carries with it an equivalent quantity of anion mostly Cl^-, we are accustomed to think of NaCl as an entity. But it is no more a physiological entity than a physicochemical one.

He went on to state: "Na, K, Ca, Cl, HPO_4, each play quite different roles in physiological processes, and, as might be expected, are dealt with separately by the kidneys as far as possible." He added that the mere necessity of maintaining equivalent quantities of cations and anions in blood and urine does, however, impose a limitation upon the independent excretion of any one. Gamble (1947) quoted a case of obstruction of the pylorus of a dog by a ligature, as a result of which there was a depletion of plasma chloride quantitatively greater than sodium. He illustrated his contention that the word "salt" had no biological meaning by noting that in this instance the kidney, dealing with the plasma ions in terms of their individual requirements, secreted an intensely alkaline urine following the administration of a neutral salt, namely, sodium chloride.

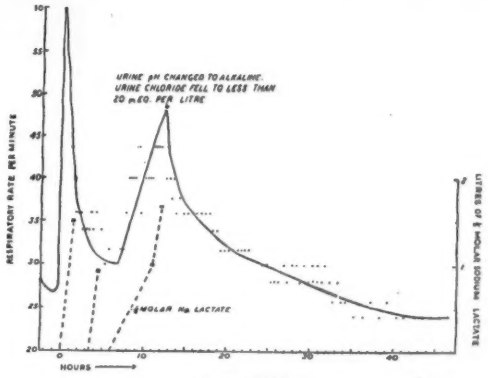
In regard to this patient, the cardinal fact was that the fistula fluid contained twice as much Na^+ as Cl^-. Therefore the level of Na^+ in the extracellular fluid would fall by a greater amount per unit time than the Cl^-. The excess of Na in the fistula fluid was secreted with an equivalent amount of bicarbonate ion. This alkaline loss would cause a stress on plasma pH control towards acidæmia.

Homœostasis.

Six facts warrant discussion. The first four could be interpreted in terms of the concept of homœostasis.

1. There was an increase in the rate and amplitude of respiration with consecuent increased excretion of carbon dioxide in the lungs. The variation in this factor appears to be related to the plasma alkali reserve, and to the intravenous administration of sodium lactate (that is, a physiologically alkaline solution being the sodium salt of an acid which is metabolized by the body). With reference to graph VII, it seems probable that the fall in respiration in the first seven hours was caused by administration of Na^+ ion.

The findings of Holler (1946) suggest an interpretation of the rise to 48 per minute which happened over the next five hours. The treatment of a patient in diabetic


URINE pH CHANGED TO ALKALINE.
URINE CHLORIDE FELL TO LESS THAN
20 m.EQ. PER LITRE
RESPIRATORY RATE PER MINUTE
1/6 MOLAR Na LACTATE
HOURS

GRAPH VII.

Respiratory rate and 1/6 molar sodium lactate infusion after surgery on the thirty-sixth day.

coma included the oral administration of sodium bicarbonate and 1/6 molar sodium lactate solution given subcutaneously. The patient developed a respiratory paralysis as the alkali reserve returned to normal. The serum K^+ at this time was 9·8 milligrammes per 100 millilitres (2·5 milliequivalents per litre). The condition was relieved by 2% KCl solution given intravenously. In the case of our patient, it is possible that the rapid intravenous administration of sodium lactate stopped the release of K^+ from cells, and, in fact, caused a transfer of K^+ from extracellular to intracellular fluid. The resultant lowering of serum K^+ caused a degree of respiratory failure. The serum K^+ measured eight hours after cessation of sodium lactate was low—13 milligrammes per 100 millilitres (3·3 milliequivalents per litre).

2. The patient excreted an acid urine. Gamble (1947) and Pitts (1945) pointed out that the continued conversion of the glomerular filtrate with plasma pH to an acid urine (*a*) avoids the useless expenditure of base as bicarbonate in that the bicarbonate content of an acid urine is many times smaller than one at plasma pH, and (*b*) causes a decrease of the base equivalence of organic acids and phosphate ions compared to plasma pH.

3. The most significant and interesting feature was the continued presence of large amounts of chloride in the urine over a period of weeks during which time the plasma chloride was probably constantly depleted below the "renal threshold". That is, the patient lost twice as much Na^+ as Cl^- from the fistula. He appeared to excrete sufficient Cl^- in the urine to keep the plasma proportions constant despite this unequal loss. The theory is submitted that the urinary chloride curve represents a renal response to the effect on the extracellular fluid of the predominant loss of sodium from

the fistula. The following observations are submitted as possible support for this theory:

(i) Evidence of a commensurate variation between the volume of fistula loss each day, and the quantity of chloride ion in the urine would tend to support this theory. A consideration of Graphs II and V over the seventeenth to the twenty-second and the thirty-seventh to the forty-fifth day periods suggests that this relation exists.

(ii) On the thirty-sixth day the extracellular sodium and bicarbonate were restored to within normal limits by the intravenous administration of 650 milliequivalents of sodium ion over a twelve-hour period. This caused a cessation of the large chloride excretion by the kidney. When the extracellular sodium level fell again, the chloride excretion recommenced. Over the time interval during which these variations occurred the plasma chloride content remained relatively constant at a level below the "renal threshold". That is, variation in extracellular sodium content was coincident with a variation in urinary chloride content.

(iii) The patient's urine on the fortieth day contained 275 milliequivalents of chloride, 205 milliequivalents of potassium, and 135 milliequivalents of sodium (Figure II). On that day the 2·4 litres of fistula fluid contained $2{\cdot}4 \times 66{\cdot}6 = 160$ milliequivalents of Na^+ in excess of Cl^-, whereas the urine contained an excess of $1{\cdot}8 \times 77 = 140$ milliequivalents of Cl^- relative to Na^+.

(iv) If the Cl^- excretion compensated for the excess Na^+ lost from the fistula, the ratio of these two ions in the plasma should remain constant.

On the thirty-seventh day plasma values were Cl = 82·7 and Na = 148·7 milliequivalents per litre with the ratio $\frac{Cl_p}{Na_p} = 0{\cdot}56$. On the forty-second day this ratio was $\frac{80}{138{\cdot}3}$ milliequivalents per litre = 0·58. On the forty-fifth day this ratio was $\frac{91{\cdot}9}{129{\cdot}1}$ milliequivalents per litre = 0·71.

Over this period from the thirty-seventh to the forty-second day 11·5 litres of fistula fluid were lost containing $11{\cdot}5 \times 66{\cdot}6 = 766$ milliequivalents of sodium in excess of chloride—this is equivalent to an excess of $\frac{766}{14}$, which is equivalent to 54·7 milliequivalents per litre of extracellular fluid if one assumes the latter to have an approximate volume of 14 litres.

Yet the ratio of chloride to sodium remained comparatively constant. The maintenance of this remarkable constant $\frac{Cl}{Na}$ ratio was clearly effected by compensatory changes in the renal excretion of these ions, as may be seen in Graph V. The ratio on the forty-fifth day had increased due to a rise in chloride—this was possibly a terminal event, in that the circulatory failure caused a breakdown in the compensatory mechanism (Graph V).

A relation can be seen between the fistula loss (stress) and the urinary chloride and respiratory rate (response) from the thirty-seventh to the forty-second day. It is then interesting to observe the respiratory rate when the final circulatory failure caused a relative failure of Cl excretion, and the level of Cl and the $\frac{Cl}{Na}$ ratio rose in the plasma.

4. The volume of urine ranged from 0·5 to 2·0 litres daily. It was interesting to observe that normal or large volumes of urine were often excreted at times when peripheral circulatory failure was impending. This supports the clinical importance of Marriott's (1947) emphasis that a normal urine volume is not necessarily an indication of normal extracellular biochemistry, and may in fact represent a compensatory mechanism to maintain osmotic pressure (Verney, 1946).

5. There was a rise in extracellular potassium (Graph IV). The studies of Guest and Rapoport (1942) on the acid-base composition of blood cells in diabetic coma suggest that a factor in the release of K^+ from intracellular fluid was the decrease of base equivalence of hæmoglobin and organic phosphates observed to occur with decrease in plasma pH.

Over the forty-five day period, the patient was given up to six complete changes of extracellular fluid by the intravenous route. Subsequent studies have shown that the failure to administer K^+ during this time was a major therapeutic error.

6. A considerable quantitative range of renal behaviour would be possible within the terms of the formulation of ionic homœostasis made in section (3). That is, if three litres of duodenal fistula fluid were lost in a day, ionic homœostasis would be maintained if the kidney excreted three litres of urine containing exactly the converse concentration of Cl^- and Na^+. However, because of the necessity of water conservation, a more effective mechanism would be to excrete less urine, but with a higher concentration of Cl^-, and a lower concentration of Na^+, so that the excess Cl^- arithmetically balanced the excess Na^+ loss from the fistula. The most effective mechanism would be if the kidney excreted no Na^+, and a sufficient amount of Cl^- to balance the excess Na^+ loss from the fistula. A major factor in the operation of such a mechanism would be the capacity of the kidney for enzymic manufacture of the cation NH_4^+. Determinations made during the last five days of life showed that, despite the acidæmia, the NH_4^+ excretion was small—not more than 10 milliequivalents per litre. The failure of this mechanism is reflected in the fact that the kidney, in excreting an excess of Cl^-, was not wholly effective in conserving the depleted Na^+ ion (Figure II). Another interesting fact was that although the urine was acid when collected, it constantly became alkaline on exposure to the air. This was probably caused by release of carbon dioxide.

Using a simple analogy, the extracellular fluid (20% of body weight) might be represented in a tank containing approximately 14 litres (Figure II). From one outlet valve (duodenal fistula) a fluid is lost containing twice as much Na as Cl. Despite the loss of 12 litres of this over a six-day period, the ratio $\frac{Cl}{Na}$ in the tank remained comparatively constant. The explanation appears to be that from another outlet valve (the kidney) a fluid is lost containing a sufficient excess of Cl^- relative to Na^+. The cation used in this process is K^+, which was coincidentally available because of its release from intracellular fluid.

There is evidence that the clinical stress necessary to produce the above type of renal behaviour need not be of the magnitude of a post-gastrectomy type of duodenal fistula. In Case IV of Bick and Wood's paper (1941) on "Biochemical Changes in Paralytic Ileus and Intestinal Obstruction" it may be observed that on the fourth post-operative day the plasma bicarbonate content was 22 milliequivalents per litre, the plasma chloride 75 milliequivalents per litre, and the urinary chloride 85 milliequivalents per litre; on the fifth post-operative day the plasma bicarbonate had fallen to 17 milliequivalents per litre, the plasma chloride to 66 milliequivalents per litre, yet the average chloride content of the urine was 126 milliequivalents per litre.

The question arises, "What specific cause acted at the renal level to determine a large excretion of chloride despite a plasma level below the 'renal threshold'?" Three possibilities might be considered:

(i) That a decrease in plasma pH was the cause. In the absence of direct measurement, the assumption of a decrease in plasma pH is based on (*a*) the volume, ionic proportions, and measured pH of the fistula fluid; (*b*) the behaviour of the respiratory centre; (*c*) decrease in plasma pH, which has often been observed clinically when Na^+ in excess of Cl is lost to a lesser degree than in a duodenal fistula.

(ii) That the kidney tubules respond to variation in the $\frac{Cl}{Na}$ ratio of the glomerular filtrate. Now the $\frac{Cl}{Na}$ ratio is a convenient aspect of ionic homœostasis to consider

when Na^+ and Cl^- loss is not equal, and when there are associated changes in total volume of the extracellular fluid. However, the question arises whether it has any direct physiological significance except in so far that changes in it may parallel variation in important factors, for example, hydrogen ion concentration. The normal $\frac{Cl}{Na}$ ratio in the plasma is 0·72 to 0·75. It is probable that the ratio on the thirty-seventh day of 0·56 represents a considerable deviation produced by the 650 milliequivalents of sodium ion which had been given intravenously. It is very significant that over the next five days the kidney maintained the ratio constant at this "low" level. It did not (*a*) adjust the ratio to "normal" by excreting the Na^+; (*b*) allow the ratio to return to "normal" by failing to excrete the depleted Cl^- ion despite the fistula loss, in that either of these processes would probably have been a severe strain on plasma pH control.

(iii) Through a number of mechanisms the fistula loss caused the release of K^+ from cells. The excretion of this excess of K^+ in the extracellular fluid demanded the simultaneous removal of an equivalent amount of anion, namely, Cl^-. The problem as to whether the presence of K^+ in the urine was causative or coincident to Cl^- excretion will be discussed in a later paper.

Conclusions.

Although it is important that observations on one patient be accepted with reserve, it can be stated that commensurate variations over a wide range were observed over a period of weeks. This is considered a form of control in biological experiment. Moreover, prior to the development of the fistula, chloride virtually disappeared from the urine when the plasma level was lowered by vomiting—that is, Cl^- was lost in excess of Na^+.

Homer Smith (1937) states that though the evidence in man is too slight to permit a definite conclusion, a notable exception such as occurs in the elasmobranch fishes engenders caution against accepting osmotic pressure *per se* as the essential goal of body fluid regulation. He does, however, summarize certain of his conclusions on renal physiology by stating that the kidney

> tends to maintain a specific pattern of various ions in the plasma, conserving each separately when the supply is deficient, excreting each separately when the supply is excessive. But the composition of the plasma in respect to total electrolytes and water appears to take precedence over the regulation of specific ions and subsidiary processes such as maintenance of the H ion concentration.

The renal behaviour in this patient would seem to differ from this view. The chloride excretion, associated with an equivalent amount of cation, continued despite a diminished total electrolyte content of the extracellular fluid sufficient to cause a circulatory failure. Moreover, this excretion in a patient already grossly depleted in total ions was doubtless a major factor contributing to the fall in plasma osmotic pressure and resultant circulatory failure. That is, the crucial point of this discussion is to consider what the effect on the pH control of the extracellular fluid would have been had the capacities of the kidney, in dealing with Cl^- ion, been limited to a mode of behaviour such as is implied by the words "renal threshold". However, under the extreme situation presented to it by a duodenal fistula, the renal mechanism does not seem wholly effective in the sense that maintenance of homœostasis in this regard compromised osmotic control to a degree dangerous to life. This problem will be considered in more detail in a subsequent paper.

Clinically, it would seem that Marriott's (1947) emphasis on the osmotic effects of the loss of extracellular electrolytes is to be supported, but his diagnostic inference that the quantity of chloride in the urine is a simple and direct relation to the quantity in the extracellular fluid needs reconsideration. There is evidence (Sanchez-Vegas and Collins, 1946; Marriott, 1947) that the Fantus test (1936) is a reliable criterion when Na^+ and Cl^- loss is balanced, or when Cl^- is lost in excess of Na^+. However, when Na^+ is lost in excess of Cl^-, diagnosis and therapy should not be based on the assumption of a simple relation. The first step in deciding replacement therapy should be analysis of the material which the body is losing; for example, chloride and alkali reserve readings on intestinal aspiration can be expressed in the diagrammatic form introduced by Professor Gamble.

Summary.

1. A patient lost twice as much Na^+ as Cl^- from a duodenal fistula. He maintained homœostasis of the extracellular fluid in this regard by excreting a sufficient excess of Cl^- relative to Na^+ in the urine (Figure II).

2. The kidney did this despite a plasma chloride depleted below the "renal threshold" (Graphs IV and V).

3. It is possible that either plasma pH or the $\frac{Cl}{Na}$ ratio of the glomerular filtrate is a factor acting at the renal tubular level to determine the excretion of chloride.

4. It is probable that renal tubular behaviour towards Cl^- ion should be considered relative to the stress which the experimental technique used places on the Na^+ ion.

5. Marriott's suggested use of the Fantus test for diagnosing ionic depletion is not completely reliable when Na^+ is lost from the body in excess of Cl^-.

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RHEUMATOID ARTHRITIS AND MONARTICULAR TRAUMA.[1]

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In a recent report of ten cases of rheumatoid arthritis precipitated by injury to a single joint (Kelly, 1948), the order of involvement of the joints was analysed. Two standard patterns were seen: (i) spread to the symmetrically opposite joint; (ii) spread to a neighbouring joint, with development of symmetrical patterns.

In the following 14 cases the patients—none of whom had had rheumatism before the injury—tell similar stories. In Cases XI and XII—injuries to the back—the site of the damage could not be identified, and in Cases XIII and XIV the onset of the arthritis was related to overstrain of several joints. In the first ten cases, however, the injury was confined to a single joint; in five of these (Cases II, IV, V, VI and VIII) the disease spread first to the symmetrically opposite joint, and in the others symmetrical patterns developed early.

Case I.—A.K., a woman, aged fifty-one years, early in 1945 injured her left knee in a fall and it remained swollen. Two months later it was manipulated by a bone-setter. Then pains were felt in the back, the shoulders and the right knee. Now she has pains in her hands and feet, with intermittent painful swelling of the wrists and the left knee.

Case II.—R.M., a woman, aged forty-five years, stated that fifteen years ago the right knee remained swollen for six months after an injury; then the left knee became painful. The pain spread to the back, the feet and the fingers, and the interphalangeal joints gradually became deformed. In May, 1948, the knees were painful, with limitation of flexion and extension of the right knee. In January, 1949, there was pain in the left knee only, with limitation of flexion and extension.

Case III.—T.C.B., a man, aged forty-eight years, states that after a fall when he was eight years old his left knee swelled and remained grossly distended. Tuberculosis was diagnosed. After many months the swelling spread to his left foot, right knee and right foot. Blisters developed on the right foot, which became gangrenous, and amputation was performed above the knee. His back became stiff and many joints ankylosed.

Case IV.—M.E., a girl, aged eighteen years, twisted her left knee when dancing, and it was painful for a few minutes. Next morning a painful swelling had appeared. Two weeks later the right knee swelled. A year later the wrists, toes and right hip were involved and she was unable to walk because of flexion contractures of the knees.

Case V.—L.S., a man, aged forty-five years, sustained a fracture involving the right elbow joint in May, 1945. Six weeks later, when the injured joint had practically recovered, pains were felt in the left elbow, the knees and the back. Most of the joints became painful and stiff, the feet and ankles being especially painful. Steady improvement took place, and in November, 1948, the disability was confined to the left hand and wrist, with swelling and stiffness of the fingers.

Case VI.—C.G.C., a woman, aged forty-four years, in August, 1945, twisted her right thumb and the metacarpophalangeal joint remained tender and painful. After three weeks the left thumb became painful; then the wrists and the joints of the fingers swelled. After being incapacitated for eighteen months she began to improve and for a year was perfectly well. In June, 1948, after an attack of influenza, she felt pains in her elbows, arms, shoulders, knees, ankles and metatarsal joints. In November, 1948, many finger joints were painful and swollen, and pains were felt in the left shoulder and the right knee.

Case VII.—W.J.A., a man, aged thirty-six years, in 1937 sustained a small wound of his right thenar eminence; the right wrist then swelled and was very painful. His left shoulder was injured in a fall; then pains were felt in both shoulders and the left wrist. His back was very painful for two years and his knees and hips were painful for a time. In October, 1948, he still had pains in his hands, wrists, shoulders and feet, with intermittent swelling of phalangeal and carpal joints.

Case VIII.—W.O., a man, aged twenty-seven years, in 1936 fractured his left carpal scaphoid, which did not unite, though it was drilled several times. Two years later the left wrist swelled; then the right wrist became painful and swollen. The process extended to the left elbow, metacarpo-phalangeal joints of both hands, knees and ankles. The disease fluctuated for some time, then gradually subsided. In June, 1948, there was little sign of arthritis and there had been no articular swelling for six months.

Case IX.—G.W., a woman, aged thirty-six years, in 1936 stubbed a big toe and afterwards the metatarso-phalangeal joint was sore and swollen. After three weeks both hands became painful, with swelling of the metacarpo-phalangeal joints. For a year the arthritis persisted; then improvement occurred and for ten years she was troubled only with transient pains here and there. In July, 1948, the wrists became painful; for six months she has been attending the arthritis clinic of the Royal Melbourne Hospital with painful swelling of the wrists and pain in the metatarso-phalangeal joints of both feet.

Case X.—J.R.W., a man, aged sixty-five years, in September, 1946, fell and injured his right elbow, which became stiff and painful, and the little finger went numb for a time. Two weeks later the finger joints of both hands swelled and soon afterwards the feet followed suit; then the shoulders and the knees were involved. At present many joints are diseased, but the condition of the hands and feet is worst.

Case XI.—A.H., a woman, aged forty-five years, in 1939 fell out of a cart and injured the thoracic part of her spine, which remained painful. In 1944 the pains became continuous and radiated to the front of the chest and dorsal kyphosis appeared. In October, 1947, the left knee swelled, and in July, 1948, the left shoulder became stiff and painful.

Case XII.—M.O'C., a woman, aged twenty-eight years, in 1935 fell off a horse and injured her back, which was continuously painful for many months. Then the wrists and some fingers became painful and swollen. In January, 1949, she had ankylosis of the right wrist and painful swelling of the left wrist. The right middle finger is now deformed and the right shoulder stiff and painful; the right metatarsal region also is painful. Occasionally she suffers from a painful back.

Case XIII.—C.C.B., a man, aged forty-six years, one week-end late in 1945 indulged in a heavy bout of unaccustomed exercise, using a cross-cut saw. His shoulders were stiff next day and gradually got worse. Then his feet became sore; then the knees and finger joints swelled. In January, 1949, many joints were involved.

Case XIV.—F.Y., a man, aged twenty-four years, in 1934 injured his right knee at football; it swelled a few times afterwards. In 1937 painful stiffness of his fingers appeared a week after the commencement of a job that involved the milking of 20 cows every night and morning—an exercise to which he was unaccustomed. He gave it up and took a job as a driver of a milk cart, and the hands improved. Three months later he sprained his right ankle springing off the cart. Then the left ankle and both knees swelled and the fingers became swollen and painful again. The disease spread and every joint was involved. Lately he has improved. His chief complaint now is of intermittent swelling of interphalangeal joints.

Discussion.

A few of these cases do not satisfy the criteria laid down by Ryden (1943), who would not entertain injury as a cause of chronic polyarthritis unless (i) the arthritis appeared promptly in the injured joint, (ii) other joints were involved before the injured one settled down. Most of the few writers who have mentioned the subject regard the credentials of trauma as dubious; presumably it is for this reason that so few writers have mentioned it or described cases in detail. To those quoted in my

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previous article the following may be added. Nissen and Spencer (1934) describe a patient whose heel was injured by a nail in his shoe; then the ankle became stiff and painful. The opposite ankle was involved, then the wrists and hands. The disease subsided, but twenty-five years later severe arthritis developed, with a rapid downhill course. Stoia (1947) has seen arthritis develop after war wounds to joints. Pickard (1947) states that out of 35 cases of rheumatoid arthritis in children, seven were precipitated by injury to a joint. Details of only one are supplied: injury to a knee was followed a month later by swelling of the other knee. Bille (1948) states that trauma caused three out of 65 cases of rheumatoid arthritis in children; symmetrical spread is the rule.

Of 46 reported cases in which data are provided (see Table I), the disease first spread to the opposite joint in 20. In the majority of the others symmetrical patterns developed early. It can be accepted as a general observation, therefore, that articular damage persisting after an injury is liable to generate painful swelling of other joints, more especially those symmetrically opposite.

TABLE I.

Symmetrical Spread of Arthritis after Articular Trauma.

Series.	Total Cases.	First Spread to Opposite Joint.
Nissen and Spencer (1934)	1	1
Edström (1942)	4	3
Ryden (1943)	19	6
Ropes and Bauer (1945)	1	0
Pickard (1947)	1	1
Kelly (1948)	10	4
Present series	10	5
Total	46	20

Injury as a Contributory Factor.

If injury alone can sometimes precipitate rheumatoid arthritis, then the mechanism of its action—whether alone or combined with other causes—is worthy of study at every opportunity. We should not carefully exclude trauma as a factor if it does not measure up to Ryden's criteria; we should take it into account and attempt to assess its influence. More numerous than the cases already cited are those in which (i) arthritis commences in a single joint some days after an injury that did not seem to involve it (Case XV); (ii) the injured joint has recovered before the second joint is involved (Case XIV, injury to knee; Case XVI); (iii) exacerbations of established rheumatic disease follow injury to a joint (Case VII; Case XIV, injury to ankle; Case XVII).

CASE XV.—J.W., a man, now aged seventy-five years, in 1934, after a heavy fall, was severely shaken but resumed work in a half-hour. A few days later his right wrist swelled and became very painful; then the left wrist followed suit and he was admitted to the Royal Melbourne Hospital. The process spread to the right shoulder, the left shoulder and many other joints. In December, 1948, he had not worked for eight years and most of his joints were painful, though few were deformed.

CASE XVI.—In September, 1948, after a blow on her left elbow, Mrs. M.D., aged forty-nine years, suffered from severe pain all day; it was the most painful injury she had ever sustained. The arm was quite well for five weeks, then severe continuous pain was felt in the right midhumeral region, and movements of the shoulder became limited. Three months later severe pain appeared in the left shoulder, with limitation of movement. No other joints have yet been involved, but no sign of improvement has appeared in the shoulders.

CASE XVII.—N.T., aged forty-seven years, had had rheumatoid arthritis for ten years. The shoulders were very painful, with some limitation of movement, and the wrists were deformed by gross distension of the dorsal tendon sheaths. The left knee and the ankles had been normal for some time, but the right knee was distended with fluid. This was aspirated, and three days later severe pain was felt in the left knee, with a tender cystic swelling in the popliteal region. From this pain radiated down the calf to the left ankle, which swelled a few days later.

The Channel of Invasion.

The observation that injury may cause rheumatoid arthritis is by no means new, but the mere familiarity of an unexplained phenomenon should not deter us from wondering about its cause. It has been ignored because it cannot be coordinated with the accepted view of rheumatism as an infection grafted on to a constitutional predisposition. Little attention has been devoted to the manner in which the disease process invades the human organism. Infections, we know, spread by the lymphatics and by the blood-stream, and so does malignant disease. It is presumed, therefore, that the rheumatic process spreads by the same channels. In Case VII, and in that reported by Nissen and Spencer (1934), lymphatic spread of infection could have occurred from the small wound to the adjacent joint that became involved. But the subsequent spread from joint to joint can be neither blood-borne nor lymphatic; in the known blood-borne affections symmetrical spread is rare.

Sir James Paget (1879), who wondered exceedingly about the exact symmetry of many rheumatic lesions, postulated at first an exact identity of chemical composition that rendered symmetrical structures equally attractive to circulating poisons. But he changed his opinion when he saw that the appearance of the lesions on the second side was often delayed for months or years. He states:

> It is clearly more probable that the symmetrical distribution of diseases on corresponding portions of the upper and lower extremities should depend on central nervous connections rather than on any assumed identity of chemical composition.

The only truly symmetrical structure in the body is the nervous system. The symmetrical spread of rheumatic disease, therefore, is probably guided by the nervous system.

Summary.

1. Monarticular trauma, as either a primary or a contributory factor, often plays an important part in the pathogenesis of rheumatoid arthritis.

2. The symmetrical spread of the disease suggests that the nervous system is involved.

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EPIDURAL INJECTION OF HYPERTONIC SODIUM CHLORIDE SOLUTION IN THE TREATMENT OF SCIATICA AND OTHER ROOT PAINS IN THE LOWER LIMB.

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EPIDURAL INJECTION was first used by Sicard (1901) to alleviate the pains of lumbago, sciatica and *tabes dorsalis*. He injected a solution of cocaine via the epidural route to avoid certain unpleasant sequelæ following intraspinal injection of cocaine which had previously been used for the same purpose, and he noticed that the pain of lumbago and sciatica might be relieved for as long as fourteen days after one injection.

Twenty years later Sicard (1921) used the term "funiculitis" to indicate inflammation of a nerve root in its intervertebral foramen. He considered that lumbago was a bilateral funiculitis of the second, third and fourth lumbar nerve roots, and that sciatica was a unilateral funiculitis of the third, fourth and fifth lumbar and first sacral nerve roots. For sciatica he advised epidural injection, twice weekly, of 20 cubic centimetres of saline containing two or three centigrammes of "Novocain", "Stovaine" or cocaine. He made no attempt to explain the method by which the injection gave relief.

During the next few years Sicard's view about the site of the lesion in sciatica was supported in America (Danforth and Wilson, 1925), in Italy (Putti, 1927) and in England (Feiling, 1928), and a school of thought grew up which considered that sciatica was an inflammation of one or more of the roots of the sciatic nerve, the site of the lesion being placed in the intervertebral foramen. This was funiculitis in Sicard's terminology, but the word radiculitis came to be used more commonly.

Brain and Strauss (1929) considered that most of the resulting benefit of an epidural injection was due to stretching of the nerve roots, and they advised the injection of 20 cubic centimetres of 1% procaine solution, presumably for anæsthetic purposes, followed by the injection of 60 to 80 cubic centimetres of normal saline, presumably to stretch the nerve roots. Another possible explanation of the benefit of an epidural injection was that the fluid passed out of the spinal canal through the intervertebral foramina and alongside the nerve roots, breaking down adhesions betwen the roots and their foramina as it passed out. These explanations, of course, were entirely theoretical and had no pathological foundation.

The demonstration that certain cases of sciatica were due to protrusions of the intervertebral disk (Mixter and Barr, 1934) did not alter the concept of radiculitis, but seemed to explain the numerous failures of epidural injection.

Sciatica then came to be regarded as a lesion of a nerve root, either compression of a root, usually by a protruded disk, or inflammation of a root (radiculitis). One method of treating the latter condition was by epidural injection, but it was never certain whether any good results were due to the injection or to simultaneous rest in bed.

The demonstration of the concealed disk by Dandy (1941), and his subsequent statement (1943) that in 95% of cases sciatica was due to a disk lesion (either a protruded disk or a concealed disk), did not alter the fact that many patients suffering from sciatica had previously recovered after an epidural injection; but it necessitated a reexamination of the whole question with a view to determining the mode of action of epidural injection and the indications for its use. In particular it was necessary to find out where the injected fluid went and what it did.

In one of my cases lipiodol had been injected into the epidural space for diagnostic purposes, and radiography showed that it gradually passed out of the spinal canal through the intervertebral foramina alongside the nerve roots; it seemed likely that saline followed the same path.

Suspensions of indian ink and solutions of methylene blue were injected into the epidural space at autopsy, and I found that the injected fluid remained in the epidural space and did not pass out via the intervertebral foramina. During life, of course, the fluid might escape via the foramina during the hours following injection, but it could hardly break down any adhesions in so doing. It therefore seemed that the fluid remained in the epidural space and produced its effect there.

In another of my cases lipiodol had been introduced into the theca on a previous occasion for diagnostic purposes. An epidural injection was given and radiographs were taken before and during the injection. These showed that the column of lipiodol was driven upwards and narrowed in an antero-posterior direction by the injected fluid. Brain and Strauss had suggested that epidural injection acted by stretching the nerve roots; but any such effect must be of very short duration, and it seemed in these radiographs that the theca was compressed in an antero-posterior rather than in a lateral direction; antero-posterior compression of the theca would be accompanied by little if any stretching of the nerve roots.

Dandy had described the nerve root as being adherent to a concealed disk, and the more one saw of these adhesions at operation, the more convinced one became that, rather than break down these adhesions, the injected fluid would follow the path of least resistance and avoid them.

Symonds (1943) had suggested that the fluid displaced a nerve root from a protrusion; but at operation one noted that if a nerve root was pushed away from a protrusion by a probe, it would usually return to its original position when released. Furthermore, protrusions are not always present in patients with diskogenic sciatica.

If epidural injection does not act by stretching nerve roots, if it does not break down adhesions, and if it does not displace a nerve root from a protrusion, what is its mode of action? This must be explained on a pathological basis, and it is therefore necessary to describe, very briefly, the pathology of sciatica.

Sciatica is a root pain affecting the fifth lumbar or the first sacral nerve root, or both. In the vast majority of cases such root pains are due to lesions of the fourth and fifth lumbar intervertebral disks, either protrusion of a disk or degeneration of a disk—a term which I prefer as being more descriptive than "concealed disk". Root pains affecting the upper lumbar nerves are most commonly due to similar lesions in the other lumbar disks. The characteristics of these various root pains have been described previously (Young, 1945, 1948). Here it need only be stated that these root pains are accompanied by neurological symptoms (tingling or numbness) or signs (motor, sensory or reflex disturbance).

In the absence of such neurological symptoms or signs pain which radiates from the back to the lower limb is possibly a referred pain, and in such cases it has been my experience that epidural injection is valueless.

In protrusion of a disk root pain would appear to be due to compression of the nerve root by the protrusion of stretching of the root over the protrusion. The classical sign of a protrusion of a lumbar intervertebral disk is an acquired scoliosis, usually convex on the side of the protrusion. In such cases it has also been my experience that epidural injection is valueless.

In degeneration of a disk the mechanism of root pain is not so clear. At operation in such cases the nerve root is often œdematous and adherent to the degenerated disk. McKenzie (1947) demonstrated œdema of a nerve root at autopsy, and Falconer, McGeorge and Begg (1948) have demonstrated œdema of a nerve root myelographically. These degenerated disks are excessively mobile, and it is my belief that this excessive mobility irritates the nerve root where it lies in contact with the degenerated disk and leads to œdema. In these cases there is no acquired scoliosis, and it is to patients without scoliosis that epidural injection may give relief.

Does epidural injection act by abolishing œdema of a nerve root or œdema of the tissues around a nerve root? If it does this, it must do so by osmosis. Does the fluid

remain in the epidural space long enough to reduce œdema by osmosis? Is the osmotic pressure of the injected fluid sufficient to do this? Does the fluid reduce the size of a protrusion by osmosis?

The length of time during which the fluid remains in the epidural space was determined by adding one millilitre of a 5% solution of "Prontosil" to the injected fluid and noting for how long the urine was stained by the dye. This was compared with the time during which the urine was coloured after intramuscular injection of the same amount of dye. It was found that the fluid probably remained in the epidural space for some nine to twelve hours (Table I), and there is therefore time for it to reduce œdema by osmosis or to reduce partially such œdema and break a vicious circle.

Table I

Case Number.	Time of Excretion of One Millilitre of 5% "Prontosil" Solution	
	After Intramuscular Injection.	After Epidural Injection.
I	—	19 hours.
II	—	23 hours.
III	—	18 hours.
IV	—	22 hours.
V	7 hours.	—
VI	6·5 hours.	—
VII	14 hours.	23 hours.
VIII	12 hours.	23 hours.

Professor R. D. Wright has informed me that the fluid in an œdematous nerve root would probably have an osmotic pressure equivalent to 0·7% sodium chloride solution. It is therefore probable that normal saline (0·9% sodium chloride solution) is slightly hypertonic as compared with the fluid in an œdematous nerve root, and it is possible that some of the solutions which have been used as epidural injections—for example, procaine in saline—acted as osmotic agents and reduced œdema.

I found that pieces of disk gain in weight when placed in 2·5% solutions of sodium chloride; so epidural injection does not act by reducing the size of a protrusion by osmosis, and it has been noted previously that patients with sciatica and acquired scoliosis—that is, patients with protruded disks—derive no benefit from epidural injection. On the contrary, it is possible that a protrusion may increase in size as a result of such treatment.

In the middle of 1946 I began to treat sciatica and other root pains thought to be due to degeneration of a lumbar intervertebral disk by injecting hypertonic saline into the epidural space to reduce œdema of a nerve root. At first 1·5% and later 2% and 2·5% solutions of sodium chloride were used in amounts of 50 and 60 millilitres. The injection is given under "Pentothal" anæsthesia to avoid pain, and no force is used.

A mistake in technique in the treatment of one of the first patients seemed to confirm the idea that the epidural injection of saline acted as an osmotic agent. My syringe and needle were wrapped in a piece of linen, boiled, brought in by a nurse and placed in a sterile bowl. I did not notice that the water from the linen had drained into the bowl. Subsequently 50 millilitres of 1·5% sodium chloride solution were poured into this bowl, where it was diluted by the water. After I had injected fifty millilitres I realized that there was more fluid left in the bowl. This was measured and found to be 50 millilitres also, so that I had injected 50 millilitres of 0·75% sodium chloride solution. The patient was no better after this injection. Three days later 50 millilitres of 1·5% sodium chloride solution were injected under "Pentothal" anæsthesia and the patient woke up free of pain some hours later. Thus his pain had been relieved by 1·5% sodium chloride solution but not by 0·75%.

Other clinical experiences also support the belief that osmosis is the means by which the pain is relieved. A patient who regained consciousness half an hour after the injection stated that he still had pain in the lower limb; but it gradually disappeared during the next hour.

Occasionally one has a patient whose pain is relieved by one injection and disappears with a second.

A patient with constant acute sciatic pain of twelve days' duration was given an epidural injection of 50 millilitres of 2% sodium chloride solution under "Pentothal" anæsthesia. On regaining consciousness some hours later he was free of pain, but this recurred each night for the next six nights. A constant acute pain had been replaced by a nocturnal pain, and this was immediately abolished by a second epidural injection.

Disappearance of sciatic pain in stages such as this could be explained by partial and then complete relief of œdema of a nerve root.

It is not easy to assess results in cases of sciatica, for it is well known that the disease is subject to spontaneous remission and exacerbation and that rest alone will often bring about a remission. This must constantly be kept in mind in attempts to evaluate any method of treatment.

It has been noted that epidural injection frequently has no effect on pain in the back or in the upper part of the buttock. Pain in these situations is possibly not due to nerve root involvement and has not been considered in the assessing of results.

During the last two years I have used hypertonic saline in an attempt to reduce œdema of a nerve root in 101 cases of root pain in the lower limb without scoliosis. Surgical experience has taught us that these patients usually have a degenerated disk with an œdematous nerve root or a small protrusion. These patients may be subdivided into two groups.

In the first group the root pain was not present when the patient was resting, but occurred only in certain postures or with certain movements. Twenty-seven such patients were treated with epidural injection of hypertonic saline and rest in bed for a week; eight of them then obtained relief; but unfortunately it is not possible to determine whether the relief was due to the injection or the rest in bed. In these cases the symptoms can be explained on the basis of a small protrusion which increases in size when the erect position is assumed, and perhaps this explains the small percentage of success in this group.

In the second group the root pain was constant and not relieved by previous bed rest. Such symptoms could be due to œdema of a nerve root. In these cases epidural injection was not considered to have given relief unless there was pronounced relief of pain in the lower limb within twenty-four hours, or unless there was some obvious and immediate change in the type of pain (for example, a constant pain changed to a nocturnal pain) and complete relief after a second injection. Of 71 patients with constant root pain, 41 were promptly relieved of the pain in the lower limb by epidural injection of hypertonic saline. Some of the failures in this group may be due to incorrect insertion of the needle, others perhaps to the presence of small protrusions. Since I have been using this method of treatment patients with degenerated disks and œdematous nerve roots have seldom needed surgical treatment, and it seems reasonable to conclude that hypertonic saline has been effective in such cases.

Thus it has been my experience that epidural injection will give relief only to patients with neurological symptoms or signs and without any scoliosis convex to the side of the root pain, and probably only to patients with constant pain; but it will be seen that even in such a carefully selected group epidural injection will fail to give relief in 40% of cases.

It must be emphasized that epidural injection of hypertonic sodium chloride solution can probably only reduce œdema of a nerve root. It cannot influence the underlying disk degeneration which causes the low-back pain, and which will still require treatment if epidural injection relieves the root pain. The treatment of such disk degeneration has been described previously (Young, 1946).

Summary.

It is suggested that epidural injection of hypertonic sodium chloride solution acts by reducing or abolishing œdema of a nerve root by osmosis.

Epidural injection of hypertonic sodium chloride solution is not likely to be of use if there are no symptoms or

signs of nerve root involvement or if scoliosis convex to the painful side is present.

Epidural injection of hypertonic sodium chloride solution is probably not effective in cases of root pain in the lower limb unaccompanied by scoliosis, if the root pain occurs only in certain postures or with certain movements.

Epidural injection of hypertonic sodium chloride solution is indicated in cases of constant root pain in the lower limb provided that there is no scoliosis convex to the painful side.

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CHRONIC NON-SUPPURATIVE HEPATITIS: SOME OBSERVATIONS WITH SPECIAL REFERENCE TO DIAGNOSIS, MANAGEMENT AND PROGNOSIS.

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ACUTE INFECTIOUS HEPATITIS is a virus infection, and most patients show complete and lasting recovery within three months. However, a small percentage fail to make this good recovery, a few dying early in the disease from widespread massive necrosis of liver cells, and others having a prolonged illness, often with exacerbations and remissions. This latter group is classified as suffering from "chronic hepatitis". In a previous communication (Wood *et alii,* 1948*a*) it was suggested that the chronic stage should be diagnosed when active hepatitis had been present for a period of four months or more.

It is the purpose of this paper to report the findings in a group of 14 well-established cases of chronic hepatitis, probably caused by the virus of infectious hepatitis (Wood *et alii,* 1948*a*), which has been studied by the Clinical Research Unit during the past three years. Seven of the 14 patients died during this three-year period of observation—a grave warning of the sinister nature of this disease when it assumes the chronic form. Particular reference will be made to the value of the clinical findings, biochemical tests and liver biopsy in making the diagnosis and assessing the prognosis. The ætiology and some typical case records have been discussed in a previous communication (Wood *et alii,* 1948*a*).

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Selection of Cases.

Fourteen patients suffering from chronic hepatitis were studied. The youngest was aged thirteen years and the oldest fifty-eight years (see Table I). Six of the patients were males and eight were females. With two exceptions the disease was contracted in Victoria: in one case infection undoubtedly occurred while the patient was on army service in an epidemic area in the island of New Britain, and the other patient was infected in Queensland. The period of study has been of variable length for the different patients (see Table I), and with one exception all surviving patients have been reviewed within a short period of the preparation of this report.

Method of Study.

The method of study has already been described in a previous communication (Wood *et alii,* 1948*a*) and will not be elaborated again. The biochemical tests used were standard for the whole group; they consisted of estimation of the serum bilirubin concentration, the cephalin flocculation test, the alkaline phosphatase test, estimation of the total serum protein content with the albumin-globulin ratio, and the oral hippuric acid excretion test. In 12 cases biopsy material was obtained from the liver, either by aspiration (nine cases) or at laparotomy. This was of considerable help in diagnosis and prognosis. In three cases aspiration biopsy was repeated on one or more occasions to provide further aid in prognosis. No complications have followed biopsy.

Mode of Onset and General Pattern of the Course.

The mode of onset divides these cases of chronic hepatitis into two groups. The first group contains cases in which the illness began with a definite acute attack of hepatitis (12 cases). The second group consists of cases in which the onset was insidious (two cases). In this latter group it was more difficult to establish the diagnosis. Here both the course followed by the disease and liver biopsy were of value.

The course of our cases of chronic hepatitis showed a variable pattern. Some patients died after a prolonged severe illness lasting more than four months without showing any real remission. Some had an illness of prolonged course with periods of temporary improvement interspersed with relapses, each relapse usually producing a more severe grade of liver damage until the patient died. Finally, others slowly but steadily improved in health over a period of many months despite occasional relapses, till eventually they appeared to make a complete clinical recovery. However, in some of these cases liver function tests still revealed damage to the liver, and aspiration biopsy revealed some cell necrosis and active inflammatory changes.

Signs and Symptoms when the Initial Acute Phase Passed to the Chronic Phase without Remission.

In the cases in which the disease progressed relentlessly from the acute to the chronic phase without remission, the early symptoms and signs continued—there were jaundice, flatulence, persistent aching pain in the liver and perhaps hæmorrhage, especially hæmatemesis. The liver and spleen were enlarged, firm and tender. Sometimes in the terminal stages the liver became impalpable.

Signs and Symptoms during Remission in the Chronic Phase.

The symptoms during remission in the chronic phase varied according to the course taken by the malady. At one extreme there were patients who felt almost com-

pletely well between remissions—they suffered only from occasional minor digestive upsets. However, more commonly they experienced chronic ill health. Other symptoms frequently present were flatulence, loss of appetite, abdominal distension, lassitude and amenorrhœa. The main complaint was: "I just don't feel well." They were tired and listless and had poor mental concentration. Ordinary routine work became a hardship and a strain for these unfortunate individuals. As in all chronic diseases personality changes were often seen—mainly depression and a tendency to over-anxiety about minor maladies (though the latter was sometimes occasioned by apprehension on the part of the attending physician). During a remission it was usual to detect some abnormality on physical examination, the commonest findings being an easily palpable liver and an enlarged spleen. In some of the advanced cases the liver became shrunken and impalpable owing to cellular atrophy and extensive fibrosis. There were certain similarities between the course of this disease and that of chronic nephritis, particularly in the exacerbations that occurred with the attendant risk of liver failure.

Signs and Symptoms during Relapse in the Chronic Phase.

The three commonest symptoms of relapse in our cases were an increase in jaundice (though rarely was this intense), diarrhœa of moderate severity (often a premonitory symptom), and pain in the region of the liver. The pain might be dull and dragging, or sharp and even colicky. These were commonly followed by flatulence, nausea and sometimes vomiting, together with a feeling of intense misery. Examination revealed the patient to be moderately jaundiced, with an anxious expression. A low-grade fever and a rapid pulse rate were present. Usually the liver was readily palpable, and in most cases the spleen was enlarged two or three centimetres below the left costal margin. Ascites often occurred. Other signs which might be noted were vascular "spiders", pleural effusion and drowsiness, the last-named being a warning of impending liver failure.

The Course.

In the 14 cases studied the course varied considerably. The most severe form of the disease, the severe non-remitting type, was shown in Case V, in which the onset was with hæmorrhage followed after two months by deep jaundice. The jaundice persisted until death occurred six months later. During this time there was a steady deterioration with loss of weight, ascites, pleural effusion and hæmorrhages. The ascites required frequent tapping.

Some patients showed severe symptoms during the initial attack, giving a clinical picture of liver failure with drowsiness, vomiting, ascites and some degree of peripheral circulatory failure. Here the prognosis was grave, but the patient might survive, definite evidence of liver damage being left. One such patient (Case III) now appears to be making a satisfactory recovery after twelve months.

In the second form of the disease, chronic relapsing hepatitis, attacks of jaundice recurred several months after the initial illness. Usually, however, some symptoms and signs of liver disease had persisted after the original acute attack. Sometimes the onset of the illness had been insidious. Some of our patients showed gradual recovery, the relapses becoming less frequent and less severe. The patient improved in general appearance and the physical signs and results of biochemical tests approached normal. On the other hand, some patients had only temporary remissions, the whole trend of the disease being downhill until death occurred in hepatic coma.

From the study of this group of patients it does seem that hæmorrhage, intercurrent infections, surgical operations and pregnancy may cause a relapse or even precipitate liver failure. Of these four factors the most ominous is hæmorrhage, particularly from œsophageal varices. The effect of hæmorrhage on an already damaged liver is to produce further, and frequently extensive, death of liver cells. Liver failure ensues. This is probably due to the effect of sudden anoxia on the regenerating hepatic parenchyma. A similar happening may be encountered in the terminal stages of other chronic liver diseases, particularly in the nutritional group (Parsons, Turner and Wood, 1949).

If the hæmorrhage is copious then the prognosis is grave and coma often supervenes in forty-eight hours.

Biochemical Findings.

There is no specific test for infectious hepatitis. However, it has been found that in both the acute and chronic phases of the illness there is a definite pattern of results, which are of considerable value in establishing the diagnosis of the disease and determining its severity. Moreover, serial tests may help in following the progress (Wood *et alii*, 1948*a*; Parsons, Turner and Wood, 1949). It is not proposed to describe in detail the abnormal results that may be found but to indicate the tests which we found to be of the greatest value in diagnosis and prognosis. Serum bilirubin estimations aided in following the course of chronic liver disease—this was the main value of the test. The level of alkaline phosphatase in the serum was usually raised, but only to a moderate degree, in most cases ranging between 14 and 30 units. The highest reading encountered in this series was 47 units. This test was of considerable value in excluding jaundice due to chronic obstruction of the common bile duct when the level was usually well above 40 units (Wood *et alii*, 1948*a*; Parsons, Turner and Wood, 1949; Wood *et alii*, 1948*b*). The oral hippuric acid excretion gave no information that was not already available from less cumbersome tests. It is by no means a sensitive test of liver function, and the many variables introduce a considerable error.

The two most useful tests were the cephalin flocculation test and the estimation of the albumin-globulin ratio in the serum. Positive results to the cephalin flocculation test were obtained from all patients except one, whose malady was shown by his history and by biopsy to be inactive (his original attack had occurred twenty years previously). But the cephalin flocculation test is not specific for infectious hepatitis. It has been shown to give positive results in nutritional disease of the liver (Parsons, Turner and Wood, 1949) and in some other diseases in which there is an alteration in the pattern of serum proteins (Hangar, 1939). However, the persistence of a strongly positive result to the test after an acute attack of hepatitis calls for increased care and a slightly guarded prognosis on the part of the physician.

The most useful test of all was the estimation of the albumin-globulin ratio. This was also the experience of O'Brien *et alii* (1944) working at Oxford. If during the acute attack there was an inversion of the ratio, the chances of an uneventful convalescence were much reduced. Further, if this inversion persisted for over four months it was probable that the disease would persist in the chronic form. We found that the return of the albumin-globulin ratio to normal was a hopeful sign, whereas all the patients who died in our series had a reversed albumin-globulin ratio. Even where the clinical signs appeared to be improving, the persistence of this abnormal ratio reduced the chances of eventual recovery.

Pathology.

In the majority of cases of chronic hepatitis in which the onset was with a definite acute attack of hepatitis, the pathological appearance was determined by the extent of the liver cell necrosis in the original infection. It may be noted here that liver biopsy studies on American army volunteers subjected to infectious hepatitis showed that severe polygonal cell necrosis could occur without the patient's showing clinical jaundice. This may provide the explanation when the onset is insidious.

If the infection was severe, often lytic necrosis was present, extending outward from the central vein and involving whole lobules, or more commonly leaving a rim of liver cells at the periphery of lobules. In such a liver there were collapse and condensation of reticulum strands in the necrosed areas (Dible, McMichael and Sherlock,

1943), and regeneration from the surviving cells formed nodules showing a generally haphazard arrangement of cells, but occasionally tending to a concentric pattern. The nodules of parenchyma were embedded in fibrous tissue produced by proliferation of the connective tissue of portal tracts. This proliferation of fibroblasts was probably induced by the stimulus of the necrosed parenchyma. Often proliferation of bile duct epithelium was present in the new connective tissue. This regeneration might provide the subject with an adequately functioning liver, but it was common to have relapses. At these periods liver biopsy was useful to show the degree of activity of the hepatitis. Continuing activity was shown by patches of necrosis of parenchymal cells with regeneration in other portions. Regeneration was recognized by the presence of large cells with basophilic cytoplasm and multiple nuclei often containing a large nucleolus. There was also concomitant formation of new fibrous tissue, bile duct proliferation and wandering cell infiltration. At autopsy in the advanced case the liver was usually smaller than normal. Available weights in five of our cases were as follows: in three females the values ranged from 1050 to 1120 grammes (normal 1150 to 1350 grammes) and in two males the values ranged from 1100 to 1350 grammes (normal 1350 to 1550 grammes). Examination of the surface revealed nodules of irregular size—some were more than two centimetres in diameter. Inspection of the cut surface revealed a repetition of the nodular pattern throughout the entire organ. Bands of fibrous tissue, often bile-stained, encircled the nodules. In one case (Case II) regeneration of liver parenchyma was minimal and the liver at autopsy was small and tough, with a smooth surface. Histological examination showed that the bulk of the liver consisted of collagenous stroma. This case has been described in detail elsewhere (King, Parsons, Perry and Freeman, 1948).

In all cases examination of the spleen revealed the usual changes of congestive splenomegaly.

At autopsy the liver of chronic hepatitis of virus origin can usually be distinguished macroscopically from that due to malnutrition. In malnutrition the external surface has a more uniform nodularity, the nodules being rarely more than one centimetre in diameter and usually much less. In less advanced cases numerous parenchymal cells contain vacuoles of fat, thus imparting pallor to the liver.

When the portions removed at liver biopsy are compared the liver of nutritional disease of the liver is usually readily distinguished by the fat vacuoles in the parenchymal cells and by the lesser degree of fibrosis. However, in an advanced case of nutritional disease of the liver the appearance may be indistinguishable from that of chronic hepatitis of virus origin. When there is mechanical obstruction to bile ducts the essential architecture of the liver is preserved and the new fibrous tissue tends to be limited to portal tract regions and to contain many new bile duct elements. The parenchymal cells in the central zones contain much bile pigment and plugging of intralobular canaliculi is present in this area.

Diagnosis of Chronic Hepatitis.

The diagnosis of chronic hepatitis usually presented no difficulties when it followed a classical acute attack. The clinical picture of the chronic phase with persistent ill health associated with continued or recurrent jaundice, ascites, hæmorrhage and enlargement of the liver and spleen is now well known.

Difficulties may occur when the onset has been insidious, but the presence of one or more of the classical signs and symptoms just enumerated should suggest the diagnosis. Difficulty may also be experienced when an acute attack is followed by only minor symptoms, such as mild ill health, flatulent dyspepsia and tenderness over the liver. This type of case has been studied by Sherlock and Walshe (1946) in England and by Volwiler and Elliott (1948) in America.

In these doubtful cases the liver function tests may be of great value, and frequently aspiration biopsy may be necessary before the diagnosis is accepted or rejected. The indications and technique of liver biopsy have been described elsewhere (King and Perry, 1948; Parsons, Garlick and Motteram, 1948), but it should be emphasized that liver biopsy should not be attempted when there is evidence of existing liver failure or when a lowered prothrombin index fails to respond to vitamin *K*.

When the diagnosis of obstructive jaundice has to be considered the position may be difficult. The presence of splenomegaly and ascites with a history of prolonged ill health does not favour a mechanical obstruction, but splenomegaly has been observed in cases of biliary cirrhosis. When the chronic hepatitis takes the form of recurring attacks of jaundice with the passage of pale stools and dark urine, biochemical tests are necessary. Even here the presence of superadded cholangitis may give rise to a positive response to the cephalin flocculation test, and aspiration biopsy may be required. The histological picture of the two conditions differs so greatly that the diagnosis can usually be made by biopsy. However, equivocal findings are sometimes encountered.

Nutritional disease of the liver may sometimes be complicated by jaundice, and here the history, clinical examination and even biochemical findings may not provide sufficient information to give the diagnosis. In this disease, too, there is frequently a strongly positive response to the cephalin flocculation test and the albumin-globulin ratio is reversed (Parsons, Turner and Wood, 1949). It has already been noted that the histological picture in advanced nutritional disease of the liver may resemble chronic virus hepatitis.

Prognosis.

In our series of 14 well-established cases of chronic hepatitis there were seven deaths—a figure slightly greater than that reported by other countries (Sherlock, 1948; Bjorneboe *et alii*, 1948). This high mortality rate has been most distressing to us, especially as it has occurred amongst the young adults (see Table I). However, two patients who subsequently "recovered" actually had clinical evidence of liver failure during the course of their acute attack (it is important to treat these attacks energetically). While there is no cause for optimism, the physician should not despair, for undoubtedly in some cases the disease process slowly abates, leaving a scarred liver which is still capable of carrying out its function, provided it is shielded from further insults (Case XIV).

The following are features in the original attack to be regarded as being of serious importance. (i) The presence of deep jaundice for a period exceeding three months. This is usually of serious import; but two patients are showing slow improvement two to three years after the onset (Cases VIII and XIII). (ii) Hæmorrhagic episodes. Those patients suffering frequent or severe epistaxis or hæmatemesis during the acute phase did not do well. (iii) The presence of ascites. This is a serious sign, but good recovery sometimes occurred. (iv) Reversal of the albumin-globulin ratio. As was previously stated, inversion of the albumin-globulin ratio is a serious sign in the acute phase of the illness. Even when this occurs good recovery may still take place (Cases I and XIII), but not unless the ratio returns to normal.

During the chronic phase any of the following factors may bring on a relapse: (i) Complicating infections; these are particularly to be feared. (ii) Pregnancy; one of our patients relapsed during pregnancy. Hysterotomy with sterilization was necessary as a life-saving measure. It is most unwise to allow these patients to become pregnant until exhaustive clinical, biochemical and probably histological examinations have been carried out over a long period. However, should the patient become pregnant and the undoubted signs of active chronic hepatitis be present, then we consider that the pregnancy should be terminated. (iii) Excessive physical and mental fatigue; this appears to be a source of relapse. Strenuous work or exercise must be forbidden while active disease remains. However, gentle exercise is to be encouraged during remission. (iv) Massive hæmorrhage, usually from œsophageal varices; this is a complication of grave import. Five of the seven deaths in our series were preceded by

TABLE I.

Summary of Fourteen Cases of Chronic Non-Suppurative Hepatitis.

Case Number.	Patient's Initials.	Sex.	Age. (Years.)	Mode of Onset of Disease.	Duration of Disease.	Outcome.	Comments.
I	A.G.	M.	58	Acute.	18 months.	Quiescent.	Subacute massive necrosis with original attack.
II	P.C.	M.	19	Acute.	10 months.	Death.	
III	A.F.	M.	40	Acute.	12 months.	Active.	Subacute massive necrosis with original attack.
IV	E.F.	F.	15	Insidious.	5 years.	Death.	
V	C.F.	M.	28	Acute.	8 months.	Death.	Jaundice first developed after three months' hæmorrhage and ill-health.
VI	P.F.	F.	22	Acute.	5 years.	Death.	
VII	F.G.	M.	28	Acute.	2 years.	Death.	
VIII	M.H.	F.	18	Acute.	4 years.	Quiescent.	
IX	E.H.	F.	47	Acute.	4 years.	Healed.	Short recurring attacks with complete recovery.
X	N.K.	F.	30	Acute.	8 months.	Death.	
XI	A.M.	F.	33	Acute.	6 years.	Quiescent.	Hysterotomy performed owing to activity of hepatitis.
XII	D.S.	F.	14	Insidious.	15 months.	Death.	Presenting symptom was hæmorrhage.
XIII	M.S.	F.	15	Acute.	30 months.	Active.	Steadily improving.
XIV	A.W. ..	M.	27	Acute.	20 years.	Probably healed.	Last recurrence July 27, 1947 (18 years after initial illness).

hæmorrhage. The usual happening was for such a hæmorrhage to be followed by coma in twenty-four to forty-eight hours and for death to ensue in the succeeding twenty-four hours.

Treatment.

As in chronic nephritis, treatment entails treating the patient and not the disease. It may be that a virus infection of the liver is still present, but so far no specific treatment is available. The main treatment should be dietetic, though experience has not provided convincing evidence that this has any beneficial effect on the inflammatory changes in the liver. The only real evidence in favour of diet comes from animal experiments by Best and his colleagues (1948), and it appears worth while to persist with it. Choline and methionine have not been used as added supplements in the present series, since the diet was planned to contain these substances in adequate amounts (milk, cheese, eggs). The patient should be warned against over-fatigue and instructed to report any illness, no matter how trivial it may appear to be. Any infection should be energetically treated with suitable antibiotics. It is probably wise to avoid sulphonamides in large dosage. Liver failure should be treated by the intravenous drip administration of glucose and saline solution, serum and blood as indicated. We have given casein hydrolysate without much success.

We have encountered cases in which an acute attack has been followed by vague abdominal symptoms. The liver is tender and may just be palpable on inspiration. Liver function tests give normal results, and in numerous cases a liver biopsy has revealed normal architecture. The physician should be on his guard not to diagnose these people as suffering from chronic hepatitis. They should be reassured, as there is no evidence of liver disease (Sherlock and Walshe, 1946; Volwiler and Elliott, 1948).

Summary.

1. Fourteen well-established cases of chronic hepatitis probably due to virus infection have been studied by clinical observation, liver function tests and aspiration biopsy of the liver.

2. This study has extended over a period of three years and during this time seven of the 14 patients have died from liver failure, usually following hæmatemesis or a superimposed acute infection.

3. In 12 cases the illness began with a definite acute attack of hepatitis, and in two cases the onset was insidious.

4. The course varied considerably. In the severe non-remitting type deep jaundice and cachexia persisted for over three months. In the chronic relapsing type attacks of jaundice recurred several months after the initial illness.

5. The outstanding symptoms and signs in the chronic phase were chronic ill health, jaundice (often slight) and splenomegaly. The liver was usually palpable, but sometimes it became impalpable late in the disease. Ascites and massive hæmorrhage (especially hæmatemesis) were of serious import.

6. The most valuable chemical tests were estimation of the albumin-globulin ratio, the cephalin flocculation test, the alkaline phosphatase estimation and the serum bilirubin test.

7. Aspiration biopsy of the liver was of value in indicating the presence and severity of the hepatitis. It also aided in excluding other forms of hepatitis, notably nutritional disease of the liver and biliary cirrhosis.

8. There is no specific treatment for this disease. Diet, limitation of physical exertion and the energetic treatment of superimposed acute infections are of value. Liver failure should be treated with the intravenous drip administration of glucose-saline solution, serum and blood as indicated.

9. Debility following acute hepatitis is discussed.

Acknowledgements.

We are indebted to those members of the honorary medical staff of the Royal Melbourne Hospital who kindly invited us to investigate patients under their care. We also wish to acknowledge the help we have received from Professor F. M. Burnet and from our colleagues in the Clinical Research Unit.

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NON-KERATINOUS CONSTITUENTS OF HAIR.[1]

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OF all mammalian tissues the hairy coat is the most easily accessible, but with the exception of the insoluble protein keratin its biochemistry has not attracted much attention.

However, a few years ago it was observed in our laboratory in Sydney that the aqueous extract of fur contains large amounts of uric acid (Bolliger and Hardy, 1944) and glycogen (Bolliger and McDonald, 1948). An attempt was therefore made to establish the essential biochemistry of the non-keratinous constituents of fur and to correlate the findings with the process of keratinization and hair formation. The bulk of our studies were made on the clean dry fur of the rabbit, a mammal which possesses no sweat glands the secretions of which might cause interference, and which is endowed with but poorly developed sebaceous glands.

With the exception of the histological (Bolliger and McDonald, 1949) and some of the enzyme studies, these experiments were conducted mainly on the extradermal fur, which was clipped from the living or dead rabbit and then extracted with five successive portions of hot water. After filtration, the practically colourless and protein-free water extract was concentrated to a convenient volume. This slightly acid concentrate (pH 6·0) was then examined for (*a*) nitrogen-containing compounds, (*b*) nitrogen-free organic compounds, and (*c*) mineral constituents. The enzyme content (*d*) was examined on the hair itself or on a cold-water extract or on the hairless skin.

Nitrogen-Containing Compounds.

The findings for nitrogen-containing compounds are listed in Table I. The total nitrogen content of the aqueous extract as determined by the Kjeldahl method varied from 500 to 600 milligrammes *per centum*; that is to say, rabbit fur contains about 20 times the amount of non-protein nitrogen usually found in blood. The total content of solids obtained after the evaporation of the solvent, water, weighed approximately 4·0 grammes *per centum*.

Of the individual nitrogen-containing substances so far identified and estimated directly in the aqueous extract, uric acid is by far the greatest in quantity—namely, 400 to 500 milligrammes *per centum* according to Folin's method. The nitrogen content of this uric acid therefore (150 milligrammes *per centum*) represents about 25% to 30% of the total nitrogen present in the aqueous extract of rabbit fur. Ammonia nitrogen amounted to about 50 milligrammes *per centum* and urea nitrogen to about 50 milligrammes *per centum*. Amino-acid nitrogen was found to be approximately 60 milligrammes *per centum*. A paper chromatogram indicated the presence of three amino-acids, which according to their position on the chromatogram were glutamic acid, valine and leucine. Creatine (9·0 milligrammes *per centum*) and creatinine (6·0 milligrammes *per centum*) were also present in larger amounts than in blood.

[1] Read at a meeting of the Section of Chemistry, Australian and New Zealand Association for the Advancement of Science, Hobart, January 12 to 19, 1949.

With reference to the non-uric acid purine nitrogen fraction, it is pointed out that the high uric acid content of the aqueous hair extract suggested nucleic acid as its probable origin, and consequently a search was made for purines other than uric acid. As has been established in numerous metabolic experiments, nucleic acid via nucleotides and nucleosides is ultimately broken down into phosphoric acid, pentose, pyrimidines and the two purines guanine (2-amino-6-oxypurine) and adenine (6-amino-purine). By the action of enzymes these two purines are de-aminized, adenine to hypoxanthine (6-oxypurine) and guanine to xanthine (2-6-dioxypurine). The enzyme xanthine oxidase finally oxidizes hypoxanthine and xanthine to uric acid.

Thus the presence of one or several of the four purines mentioned in the aqueous extract would support the assumption that a similar chain of reactions takes place in the process of uric acid formation in fur.

The search for non-uric acid purines was carried out as follows. From the concentrated aqueous hair extract uric acid was precipitated by the addition of sulphuric acid. After the crystalline uric acid had been filtered off, the filtrate was treated with copper sulphate and sodium bisulphite. This precipitated the remaining purines in the form of a copper compound, and after this copper purine precipitate had been decomposed with hydrogen sulphide, a colourless filtrate was obtained which on evaporation yielded about 100 milligrammes *per centum* of a white solid containing 43% of nitrogen. This high nitrogen content suggested a probable mixture of adenine (N=52%), guanine (N=46%), hypoxanthine (N=41%) and xanthine (N=37%).

A microscopic examination of the precipitate revealed a mixture of the crystals, some of which resembled adenine, others hypoxanthine and xanthine. From this mixture xanthine was isolated as xanthine silver, and xanthine itself was isolated and examined spectroscopically. An absorption maximum at 270μ was found. This is typical of xanthine. It was also possible to isolate crystals of hypoxanthine silver nitrate and adenine picrate. However, further investigation will be necessary to establish definitely the identity of these compounds.

On the basis of these observations and others on enzymes which will be mentioned shortly, it is suggested that nucleic acid is the main source of the large amount of uric acid in fur.

Nitrogen-Free Organic Compounds.

Fifteen volumes of alcohol were added to the purine-free aqueous extract. This brought down an amorphous white precipitate which proved to be mainly glycogen, by its solubility, by its reaction with iodine, and by hydrolysis with mineral acids or with enzymes which all yielded glucose. The amount of glucose obtained by hydrolysis was determined and found to correspond to a glycogen content of 300 to 500 milligrammes *per centum*. However, the original aqueous extract was also found to contain 100 to 300 milligrammes *per centum* of directly reducing substances, which reacted with Benedict's reagent without previous hydrolysis, but which do not seem to be glucose, because we have not yet succeeded in obtaining the characteristic osazone.

Citric acid, partly in the form of calcium citrate, was also found to be present in the aqueous extract. Determined quantitatively by the method of Pucher, Vickery and Leavenworth (1934), 50 to 60 milligrammes of citric acid were found in 100 grammes of hair. On the addition of ferric chloride to the water extract, a yellow colour was obtained. This indicated the presence of lactic acid, which, when determined by the method of Barker and Summerson (1941), was found to be present in an approximate amount of 10 milligrammes *per centum*.

Mineral Constituents.

About 40 milligrammes *per centum* of calcium were found in rabbit fur. However, only about 200 milligrammes *per centum* of sodium were present in the fur extract, while the potassium content was found to be as high as 500 milligrammes *per centum*; 600 to 700 milligrammes *per centum* of chloride were also present, but only 10 to 15 milligrammes *per centum* of phosphorus.

Enzymes.

For the past thirty years the mammalian skin has frequently been examined for enzymes, and all the important hydrolytic enzymes have been shown to be present. In contrast to these extensive investigations on skin, however, the extradermal hair has largely been ignored. If one postulates that in the process of hair formation anything like the well-known nucleic acid metabolism occurs with uric acid as its end product, then one must assume the presence of a series of enzymes.

More than a year ago, experiments were performed on guinea-pig, rat and rabbit skin to see if the enzymes involved in the classical theory of uric acid synthesis were present, and, if they were detectable, to investigate their degree of activity (McDonald, 1948). In the first place, it was found that enzymes active in the uric acid cycle were present in the skin of our rodents, and that sufficient precursors of uric acid were present in the normal skin for some uric acid to be produced without the further addition of purines. Next, it was found that when rat skin was incubated with guanine, adenine or xanthine the uric acid content of the preparation increased by 200% to 300%. Moreover, the skin when incubated alone produced some uric acid.

From these experiments it was concluded that the skin of some rodents contains enzymes which convert guanine, adenine and xanthine into uric acid. The nature of the enzymic action suggested the presence of guanase and adenase and of an active xanthine oxidase. It had been provisionally assumed that these catalysts would be exclusively confined to the hair root and the immediately surrounding living skin tissue. The finding that the "dead" extradermal hair is also endowed with enzymes was thus somewhat surprising. A series of qualitative and quantitative investigations were commenced, and these yielded some interesting results. For example, the cold-water extract of 100 grammes of rabbit fur contained as much as 50 King-Armstrong units of phosphatase. This or part of it may in fact be the nucleotidase which splits phosphoric acid from the nucleotides, but which is also known to act as a typical phosphatase. The presence of a xanthine oxidase was established qualitatively. Dopase, the enzyme which converts 2-4 dihydroxy-phenylalamine into melanine, is also active in hair fibres. Solutions of the substrate turn brown within fifteen minutes after the addition of rabbit hair in a ratio of about 0·5 grain of hair to 50 millilitres of substrate solution.

Discussion.

If one tries to integrate the experimental findings from the water-soluble constituents of fur into the whole picture of keratinization and hair formation, one may be inclined to look upon each individual hair as a compact metabolic unit in which a thin short layer of the cellular epithelial tissue is converted into a comparatively large fibre. The hair root is undoubtedly the factory where much of this conversion occurs, some of the end or waste products of this conversion process, such as uric acid, urea and ammonia, being stored in the fibre. However, intermediary products and enzymes are found in the fibre also, and one begins to wonder if processes vital to the maintenance of the fibre do not take place in the so-called dead portion of the hair.

How can the reported findings help to explain certain aspects of hair formation?

The most obvious differences between the "purified" protein keratin and the epidermal cells from which it is formed are (i) the high degree of dehydration of keratin, (ii) the absence of cell nuclei in the keratinous structures and the absence of nucleic acid decomposition products in the keratin protein, (iii) the increased cystine and tyrosine content of the keratin.

The High Degree of Dehydration of Keratin.

In rabbit fur the water content of the hair is less than 10%, whilst the water content of the epidermal cells is from 60% to 70%. The fate of this water is not known with certainty, but it may be assumed that a portion of it becomes lost by evaporation. A certain amount, moreover, may be required for the chemical transformations which accompany the complicated process of keratinization.

The Absence of Cell Nuclei in the Keratinous Structures.

Obviously the loss of the nuclei entails the disposal of considerable amounts of desoxypentose nucleic acid. In the keratin itself no trace of this nucleic acid, or of its most characteristic degradation products the purines and the pyrimidines, can be detected. This applies as well to the pentose nucleic acid of the cytoplasm, which also leaves no obvious traces in the protein keratin formed from it. On the other hand, the aqueous extract of rabbit fur contains amounts of uric acid which, from the physiological standpoint, must be regarded as enormous. Uric acid is, of course, the generally recognized end product of nucleic acid katabolism.

Xanthine, hypoxanthine and adenine, precursors in the classical scheme of uric acid production, are also present in the hair fibre. Furthermore, some of the required enzymes have been detected in the extradermal fur and in the skin.

All these findings strongly suggest that the purines of the nucleic acid from the extruded nuclei are ultimately converted into the urates deposited in the fibre.

One may ask how much of the nucleic acid purines is recovered in hair. In the absence of determinations of nucleic acid of the non-cornified cells of the epidermis, it is difficult to make any definite statements; but to judge from measurement on other organs, it appears as if most of the nucleic acid present in these cells can be accounted for in the purine content of the aqueous extract of rabbit fur, and that apparently only a small fraction, if any at all, is metabolized or stored elsewhere.

The bulk of the pyrimidines, as elsewhere in the body, may be expected to be oxidized and ultimately recovered in part as urea. Therefore, the urea found in the water extract of hair may well be derived from the pyrimidines originally present in nucleic acid.

Phosphates, another breakdown product of nucleic acid, which occur in every nucleotide, are found in comparatively small amount (only 10 to 15 milligrammes *per centum*) expressed as phosphorus. To judge from phosphorus determinations on the ash of fur, it appears as if some phosphorus is present in the hair in a water-insoluble form. However, even when this is taken into account, one must assume disposal of nucleic acid phosphorus in a form unknown so far.

Large amounts of glycogen were found to be present in hair. This glycogen could have originated largely from the pentoses of nucleic acid, after conversion to glucose, the carbohydrate currency of the body.

The Increased Cystine and Tyrosine Content of the Keratin.

The proteins present in the living epidermis have to be rearranged in such a manner as to allow for the increased cystine and tyrosine content of keratin. This in all probability necessitates the hydrolysis of some proteins to the amino acid or polypeptide stage, and the incorporation of some of the amino acids into suitable aggregates which ultimately will make up keratin. This would leave some free amino acids or polypeptides, which either would be reabsorbed by the skin, or could, in part at least, make their appearance in the water-soluble extract of fur. Amino acids, such as valine, leucine and glutamic acid, which could be derived from the cells undergoing keratinization, are found in the aqueous extract of hair. On the other hand, no sulphur-containing amino acids or other sulphur-containing compounds have been found so far amongst the non-keratinous constituents of hair. This may indicate that all sulphur obtainable from the epidermal cells is required for the construction of the keratin molecule.

The high potassium and low sodium content may also testify to the intracellular origin of the constituents of the aqueous extract. In the body fluids this relationship between potassium and sodium is reversed.

So far reference has been made only to the fur of the healthy rabbit. With regard to uric acid and glycogen,

qualitatively similar findings have been made in other mammals including the sheep and man. However, there are pronounced quantitative differences in different species. For example, rat fur contains about 250 milligrammes *per centum*, guinea-pig fur 150 milligrammes *per centum*, dog hair 100 milligrammes *per centum* and human hair about 10 to 15 milligrammes *per centum* of uric acid.

The findings in pathological conditions examined so far include observations on skin diseases in rabbits (tinea and mange), in which the uric acid content was found to be diminished by 50%, while from human patients suffering from chronic gout hair uric acid values twice as high as normal were obtained.

In healthy specimens physiological differences may be expected between the young and the old. For example, the hair of my children contains substantial amounts of glycogen while my own hair contains none.

Summary.

An aqueous extract of rabbit fur was found to contain uric acid, xanthine, amino acids (valine, leucine and glutamic acid), urea, ammonia, creatine, creatinine, glycogen, citric and lactic acid and reducing substances, together with inorganic constituents and enzymes. Uric acid and glycogen were present in amounts as high as 500 milligrammes *per centum*.

Enzymes found in the epidermal skin by previous authors, such as phosphatases and dopase, were also encountered in the extradermal hair. In addition, enzymes involved in the classical theory of uric acid synthesis, such as guanase, adenase and xanthine oxidase, appeared to be present in the skin, the last-mentioned also in hair.

Evidence is produced that many of the non-keratinous constituents of hair are derived from nucleic acid present mainly in those epidermal nuclei which disappear in the process of keratinization. Thus the study of the most readily accessible tissue, the extradermal hair, and particularly its non-keratinous constituents, is not only of considerable physiological interest, but also affords an insight into the keratinization process.

Table I.

Approximate Nitrogen Content of Substances "Identified" in the Aqueous Extract of Rabbit Fur (Total Nitrogen Content 500 to 600 Milligrammes per Centum).

Type of Nitrogen.	Amount. (Milligrammes *per Centum*.)
Uric acid nitrogen	150
Nitrogen from other purines	50
Urea nitrogen	50
Ammonia nitrogen	50
Amino acid nitrogen	60
Creatine nitrogen	3
Creatinine nitrogen	2
Total "identified" nitrogen	365

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Reports of Cases.

A CASE OF SEVERE TETANUS TREATED WITH A CONTINUOUS INTRAVENOUS INFUSION OF "MYANESIN" AND "SODIUM PENTOTHAL".

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The reason for reporting this case of severe tetanus is to demonstrate the efficacy of "Myanesin" and "Sodium Pentothal" given by continuous intravenous infusion, in controlling the severe spasms, when heavy sedation by routine methods had failed, and the patient appeared certain to die. The use of "Myanesin" in tetanus was suggested by Belfrage,[1] and more recently by Torrens, Edwards and Wood.[2] The treatment to be described differs in several details from their methods.

Clinical Record.

V.H., a well developed male deaf mute, aged eleven years, with a weight of 72 pounds (convalescent), was admitted to the Children's Hospital, Melbourne, on January 4, 1949, at 5 p.m. Ten days before admission, he had sustained a puncture wound from a piece of wood in the dorsum of his left foot. The wound was treated with local dressings. No antitetanic serum was given. On the day before admission he developed generalized muscle spasms with head retraction, the spasms lasting ten to twenty seconds, and on the same night was unable to open his mouth or eat his evening meal. These symptoms increased in severity during the next twenty-four hours.

On examination, he was conscious but apprehensive, and was having frequent generalized spasms with head retraction, which caused him to scream shrilly and perspire profusely. In between spasms, he had severe trismus, *risus sardonicus*, abdominal rigidity and hypertonic limbs. There was a deep infected puncture wound on the dorsum of his left foot, from which pus could be expressed. His temperature, pulse, and respirations were within normal limits between spasms. There was no other abnormal finding.

Treatment was instituted in a small, darkened, single-bed ward. Antitetanic serum was given intramuscularly in small initial doses because of a skin sensitivity reaction; 228,000 U.S.A. units were given in three days. Penicillin (100,000 units) was administered intramuscularly, and 50,000 units were ordered to be given three-hourly. Paraldehyde *per rectum* and "Sodium Amytal" by the intramuscular route were given in increasing doses until the child was receiving, on January 7, 12 millilitres of paraldehyde and 0·25 gramme of "Sodium Amytal" three-hourly. The infected wound was explored, sixteen hours after commencement of treatment, and a purulent slough was found extending to a depth of 1·5 centimetres; from a swab from this was later grown *Clostridium tetani*. No foreign body was found at this time, but, during convalescence, a splinter of wood was extracted. The wound was widely opened and packed with gauze soaked in "Eusol", and 20,000 units of penicillin were injected into the surrounding tissues. A gastric tube was introduced, and a 2400 Calories per day fluid diet of milk, eggs, cream, powdered milk and "Pronutrin" (casein hydrolysate), with orange juice given separately, was fed in a volume of 2·5 litres per day. This was tolerated well.

By January 7 the child, although unconscious from sedation, was still having almost continuous spasms. His temperature was now 104° F. It was impossible to nurse him adequately, and it appeared that he would soon die from exhaustion. It was then decided to administer "Myanesin" in proportionate doses, as recommended by Torrens, Edwards and Wood.[2] "Myanesin" 0·5 gramme (five millilitres) diluted with five millilitres of sterile water was injected intravenously, with dramatic result. There was immediate relaxation of the facial, skeletal and abdominal muscles. The jaw was relaxed sufficiently to allow the carrying out of a mouth toilet, which until then had been impossible. There was no embarrassment of respiration, change in colour, or alteration of the pulse. Within ten minutes the spasms had recurred, including a severe spasm lasting five minutes. This was in contrast to the result previously reported,[2] in which there were no spasms for a period of twelve hours following a single injection of "Myanesin". A second injection was given with identical results.

It was apparent that a single intravenous injection of "Myanesin" would effect no more than temporary relief of the spasms, so a continuous intravenous infusion of "Myanesin" two grammes to 600 millilitres of one-quarter-normal saline with 5% glucose solution was commenced at a rate of 60 millilitres per hour, together with retention of the same heavy sedation of paraldehyde and "Sodium Amytal". After six hours the spasms, although less severe, were still almost continuous. It was then decided to combine "Sodium Pentothal" 0·5 gramme with "Myanesin" 1·0 gramme in 600 millilitres of glucose-saline infusion. Paraldehyde and "Sodium Amytal" were discontinued. After a few hours of infusion of this solution, the spasms had decreased in both frequency and severity. The nurse assigned to the patient was instructed to regulate the rate of drip according to the spasms. This procedure proved most effective, as the spasms, although not completely prevented, were now relatively mild and infrequent, and severe recurrences could be suppressed by simple adjustment of the drip rate. The child was now relaxed for periods of ten to fifteen minutes between minor spasms lasting half to one minute. This procedure was followed for the succeeding three days. His daily intake of fluid by intravenous infusion was approximately 1·8 to 2·4 litres containing 3·0 to 4·0 grammes of "Myanesin" and 1·5 to 2·0 grammes of "Sodium Pentothal" (1·0 gramme "Myanesin" and 0·5 gramme of "Pentothal" per 600 millilitres). General nursing measures were carried out efficiently and easily, without fear of precipitating a severe spasm. His chest remained free from abnormal physical signs, but the temperature remained elevated from 102° to 104° F.

On January 11 his condition had improved to such an extent, with mild spasms only every fifteen to thirty minutes, that it was decided to withhold "Myanesin" temporarily from the infusion and observe the effect. Rapid recurrence of spasms, however, demonstrated the inefficiency of "Sodium Pentothal" alone. On this day, seven days after administration of antitetanic serum, a generalized urticarial rash developed. This responded within twenty-four hours to "Benadryl" 50 milligrammes three times a day given by the intragastric tube.

On January 12 the intravenous site was changed for the third time in five days because of venous thrombosis. Heparin in small doses (five milligrammes) was added to each pint of infusion fluid in order to delay local venous thrombosis. Although the dose was very small, and daily blood coagulation time estimations showed an increase from four to eight minutes, the desired effect was obtained, and it was not necessary to change the site of infusion for over a week. Penicillin which had been given intramuscularly by injection was also added to the intravenous infusion fluid (40,000 units per 600 millilitres) with the object of averting intercurrent infection. Owing to more frequent spasms, "Sodium Pentothal" was increased to 0·75 gramme per 600 millilitres. The infusion fluid now contained "Sodium Pentothal" 0·75 gramme, "Myanesin" 1·0 gramme, penicillin 40,000 units, and heparin 5·0 milligrammes per 600 millilitres of one-quarter normal saline with 5% glucose solution, and was administered at a rate of 60 millilitres per hour, with increase in rate at the nurse's discretion, according to the patients' condition. The same diet was provided by intragastric drip. There appeared to be little danger of electrolyte imbalance, as the child was retaining a well-balanced fluid diet, as well as the saline given intravenously. Urinary output was good, and the results of daily urinary chloride estimations were normal. There was no clinical evidence of fluid retention, and the chest remained clinically free of abnormality.

By January 17 improvement was evident. Spasms were confined to arching of the back and elevation of the left leg. On January 18 "Myanesin" was again discontinued, this time without any increase in spasms, and on January 20 improvement was sufficient to justify reduction of "Sodium Pentothal" to 0·5 gramme per 600 millilitres of infusion fluid. During the illness, the child appeared to have lost most of his subcutaneous fat, so that the caloric value of the diet was increased to 2748 Calories per day by the addition of cream. This was tolerated well.

By January 25 failure of the intravenous flow prompted a return to intramuscular "Sodium Amytal" sedation. Recurrence of spasms, however, necessitated further intravenous "Sodium Pentothal" sedation. Another attempt to discontinue "Sodium Pentothal" on January 27 was successful, and "Sodium Amytal" 0·25 gramme, given four-hourly as necessary, controlled any undue restlessness. The total amount of "Sodium Pentothal" given was 32·75 grammes, and of "Myanesin" 40 grammes. Procaine-penicillin-in-oil, 150,000 units daily, was substituted for penicillin given by the intravenous route.

By January 28 the child was taking oral feedings, and by January 31 he was mentally alert, conversing in sign language, and showing no ill effects from three weeks' virtual anæsthesia. His temperature was normal. There was clinically no observed ill effect from either "Sodium Pentothal" or "Myanesin", apart from venous thrombosis in the immediate locality of the intravenous wound. There was no liver tenderness or enlargement, nor any clinical jaundice. Urinary excretion was unimpaired. Liver function tests (total serum protein estimation, thymol turbidity and flocculation tests, serum bilirubin and serum alkaline phosphatase estimations) all gave normal results. Hæmaturia or hæmoglobinuria did not occur.

By February 4 the child was walking with not more than 15° limitation of extension at the ankle joint. His appetite was good and he was alert mentally. The original infected wound of the foot had almost healed, and examination of another swab revealed no *Clostridium tetani*.

Although the patient had been unconscious for three weeks, with frequent spasms, the nursing was so satisfactory and simple that nothing more than a superficial abrasion developed over the sacrum. He was discharged from hospital on February 22, 1949, having made a complete recovery.

Summary.

1. A case of severe tetanus is reported. The tetanus was unusually severe, because, firstly, the continuous generalized spasms were not influenced by heavy sedation with paraldehyde and "Sodium Amytal", and secondly, the spasms lasted for a period of twenty-three days before intravenous therapy could be discontinued.

2. Single intravenous injections of "Myanesin" controlled the spasms for only ten minutes.

3. "Myanesin" 1·0 gramme and "Sodium Pentothal" 0·75 gramme per 600 millilitres of infusion fluid, given at the rate of approximately 60 millilitres per hour continuously by intravenous infusion, controlled the spasms.

4. When "Myanesin" was withheld on the fourth day of this treatment, immediate recurrence of severe spasms demonstrated the inefficacy of "Sodium Pentothal" alone.

5. The two main advantages of this method are, firstly, the ease with which the patient can be nursed adequately, and secondly, the simplicity and rapidity with which severe spasms can be controlled.

6. There was no clinical or biochemical evidence of any ill effects from the continued use of large doses of "Sodium Pentothal" for a period of twenty days, and "Myanesin" for a period of eleven days, apart from local venous thrombosis. The absence of complication was probably due to the administration of "Myanesin" in high dilution.[6]

Acknowledgements.

I wish to thank Dr. Robert Southby, honorary in-patient physician in charge of the patient, for his encouragement and permission to report the results. My thanks are also due to Dr. Cedric Vear, the resident medical officer with whom I was associated in the management of the child's illness.

Addendum.

Further experience suggests that larger doses of "Myanesin" than were used in the above case could be administered with advantage and with less sedation.[1]

Reluctance to use larger doses of "Myanesin" arose from reports of toxic effects of this drug.[5] [6] [9] However, the complete freedom from toxic effects when "Myanesin" was administered in dilute solution[6] by continuous infusion prompted the use of an increased dose in a second case of less severe tetanus in a boy aged ten years whose spasms lasted for nine days. The administration of six to eight grammes of "Myanesin" per day suppressed the spasms to such a degree that further sedation was limited to an occasional nightly dose of "Nembutal" 0·1 gramme. The child, throughout his illness, was able to feed himself and so was very easy to nurse. No toxic sequelæ from "Myanesin" occurred.

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ANTI-HISTAMINE WITHDRAWAL SYMPTOMS: REPORT OF THREE CASES.

By Alan Cherry,
Largs Bay, South Australia.

In 1942 Mrs. C. went to live in Melbourne, since when she has rarely been without hay-fever; she had never experienced it before. By 1947 she had exhausted every variety of nasal decongestant, purchased every available box of "Kleenex Tissues", and suffered the usual course of desensitizing injections. "Benadryl" at last brought relief. In October, 1947, she was stricken with a peculiar attack of giddiness, nausea and vomiting. She was examined by a consultant physician, who diagnosed her complaint as labyrinthitis, prescribed a phenobarbital and bismuth mixture and advised her to leave off "Benadryl", as her disorder might be an unexpected side-effect of that relatively unknown drug. Unfortunately her condition failed to improve—it possibly grew worse—and to add to the misery of it all, her hay-fever returned. The patient "sneaked in" a few "Benadryl" capsules, and we found, in retrospect, that whenever she took "Benadryl" the labyrinthitis ceased and *vice versa*. We assumed that she had become a little lax originally with the "Benadryl". It took nearly a fortnight to wean her off "Benadryl" in gradually decreasing doses. Since then she has tried "Antistine" and "Anthisan"—both effective in preventing her hay-fever, but both bringing on labyrinthitis symptoms on withdrawal.

Early in 1948, Mrs. D. consulted my father, who prescribed "Benadryl" capsules for an allergic skin eruption. A few days later I visited Mrs. D. in my father's absence, to find her complaining of intractable giddiness, nausea and vomiting. It appeared that her skin rash had disappeared two days previously, so she had decided to leave off the "Benadryl". Within two hours of taking "Benadryl" capsules Mrs. D. felt well again—but it took her six weeks to wean herself from this drug.

Three weeks ago Mrs. A. began taking "Anthisan" tablets for an effusion in her right knee that was thought to be secondary to an erosion of her *cervix uteri*. Her tablets expired on June 6, 1949, and on June 7 she felt giddy and violently ill. Within two hours of taking another "Anthisan" tablet her symptoms disappeared. In this case the weaning period has been very short, but the effusion in her knee continues.

Comment.

Three different anti-histamine drugs are described as causing labyrinthitis symptoms and they have been used for different types of allergic conditions. It appears that in some people a histamine labyrinthitis develops on withdrawal of the anti-histamine drug. This may possibly be due to the latter drug's replacing the host's natural resistance to histamine, so that on withdrawal of the anti-histamine drug the natural resistance takes some time to develop—hence the "weaning period". I have not tried to substantiate this hypothesis experimentally. I have spoken to the local agent for one of these anti-histamine drugs; he had never heard of the withdrawal reaction and assured me that he would make enquiries. I have not heard from his since, nor have I seen any reference to this phenomenon in the literature.

It is interesting to recall that other drugs—for example, morphine, alcohol *et cetera*—cause severe withdrawal symptoms, and it may be that this is a similar type of reaction.

Reviews.

THE LAW AND PROCEDURE AT MEETINGS IN AUSTRALIA AND NEW ZEALAND.

Joske's book on law and procedure at meetings is described by the author as "a concise guide to assist persons taking part in or who may be called upon to advise in connexion with meetings".[1] It is particularly well indexed and, being a small volume, it can be taken to meetings without difficulty. Appropriate catch words appear at the commencement of each chapter. The author has quoted authorities for his propositions of law, but these appear as footnotes, and care has been taken to avoid language that could cause difficulty to a layman. The subject is dealt with in two parts, the first being "Meetings in General" and the other "Meetings of Companies". What are legitimate amendments to a motion? What matters can be discussed on a motion for confirmation of the minutes? To what extent is a speaker at a meeting protected from an action for defamation of character? What are the more important statutory provisions as to calling of meetings of companies? What rules apply to the appointment of a proxy? Questions such as these may be readily answered by a reference to this book.

Quite apart from the more serious questions of rights being preserved by the proper conduct of a meeting, most of us have experienced too frequently the waste of time and general confusion resulting from inept chairmanship. Mr. Joske has destroyed any excuse for this sort of inefficiency.

A REASSESSMENT OF THE WORK OF LAWSON TAIT.

It is interesting to note that medical historians are beginning to recognize the worthiness of an Australian surgeon, W. J. Stewart McKay, as the authoritative biographer of that aggressive and ill-mannered pioneer of abdominal surgery, Robert Lawson Tait. No doubt the soothing influence of time and the desire to do full justice to the pathfinders of medicine who have shown originality of thought in contributing to knowledge and in enlarging the field of useful practice, may account for the awakening of interest in Tait as an historical curiosity and in the rare gifts so lavishly bestowed upon him by his admiring biographer. One criticism that might be applied to the book written by Stewart McKay nearly thirty years ago is that the inclusion of a superfluity of extraneous matter concerning ancient gynæcology, and lengthy descriptions of perineal repair operations as performed by his master and later by himself, caused the volume to assume a corpulence that was hardly warranted. Now we have a small book on Lawson Tait built up upon the Thomas Vicary Lecture delivered before the Royal College of Surgeons, England, in 1947.[2] The author, I. Harvey Flack, M.D., was prompted to give a reassessment of Tait's work, and the new publication will be welcomed by medical historians as it will help to focus more attention on the work of this pioneer surgeon and less upon his antisocial tendencies.

In arriving at an estimate of the services rendered to this country by such notorious characters as John MacArthur and William Bligh, it is essential that due consideration be given to the political, social and economic systems in vogue at the time they were enacting their dramatic scenes in the process of colonial expansion. So we must remember that Lawson Tait was playing his part in the development of modern surgery in a period of intensive intellectual activity, scientific advancement and immoderate individualism, particularly in the upper strata of society. In the nineteenth century ambitious men needed moral courage, strength of character and exceptional ability for success in any high enterprise; and, be it remembered, they had just been told by a great scientist that the survival of the fittest could be accepted as a maxim in biological progression. When, in 1870, Tait had the audacity to set himself up in practice as a surgical specialist in the provincial town of Birmingham, it may be imagined that

[1] "The Law and Procedure at Meetings in Australia and New Zealand: A Concise Guide to Assist Persons Taking Part in or who may be Called upon to Advise in Connexion with Meetings", by Percy Ernest Joske, K.C., M.A., LL.M.; Second Edition; 1949. Sydney, Melbourne and Brisbane: The Law Book Company of Australasia, Proprietary, Limited. 7" × 4½", pp. 209. Price: 12s. 6d.

[2] "Lawson Tait, 1845-1899", by I. Harvey Flack, M.D.; 1949. London: William Heinemann (Medical Books), Limited. 7¼" × 5⅜", pp. 162, with illustrations. Price: 17s. 6d.

he had to depend a great deal upon his natural self-assertiveness in order to gain his objectives.

At the same time that Tait was nonchalantly encouraging the fierce antagonism of his older colleagues in the larger centres of surgical specialism in his own country, he was able to convince the rest of the medical world that the presence of a large ovarian cyst could be no longer considered as the sole indication for resorting to abdominal section, and that an entirely new approach to surgical pathology within the sacred precincts of the abdominal cavity was being brilliantly exploited in the provincial town of Birmingham. He was able to demonstrate that there were many pathological conditions which caused prolonged suffering and frequently had a fatal termination unless they could be diagnosed early and then treated radically by surgical interference.

Besides developing his own technique for dealing with the pedicle of an ovarian cyst, Tait was the first to deal successfully with hydrosalpinx, pyosalpinx, hæmatosalpinx, hydatid cyst of the liver, the pathological gall-bladder, ovarian disease, pelvic suppuration and ectopic gestation. For these reasons William J. Mayo described him as the "Father of Abdominal Surgery", and another distinguished American surgeon of the day admitted that "in pelvic surgery Lawson Tait stood first, and taught us the best we know".

When it is remembered that Tait was born and educated and then obtained his medical qualification in Edinburgh at the time when Professor Joseph Lister was immersed in his work on the antiseptic principle in surgery, and that he was not slow to insinuate himself in the good graces of Sir James Simpson and other eminent surgical practitioners of the city, it is hard to believe that he was not well acquainted with the latest developments in the surgical treatment of open wounds. Although for some unaccountable reason he outwardly refused to see any virtue in Listerism, there is little doubt that he well understood its implications and used the knowledge to further his own efforts to perfect what we like to think of today as a faultless aseptic technique.

Tait may have been wrong-headed at times, but he was a man of wide culture and exceptional ability. Furthermore, he was possessed of a remarkable dexterity, which enabled him to find his way among pathological intricacies within the abdomen by the mere sense of touch, for there was only the dim light of the patient's bedroom and he worked without the advantages to be gained from the Trendelenburg position. He had a natural gift of expression with both the written and the spoken word, which assisted him to keep the wolf from the door in the lean years as a regular writer of editorials for a local publication, and later helped him to deal rather unmercifully with his unfriendly critics in the medical journals and at medical association meetings in London.

If Stewart McKay's estimate of Lawson Tait savours a little of suppressed hero-worship, then it may be said that Dr. Harvey Flack is not so generous in dealing with this aggressive individualist. What he means by alluding to Tait's last years of physical suffering and acrimonious debate as his "Downfall" is rather difficult to understand.

BLOOD TRANSFUSION.

In the preface to "Blood Transfusion"[1] Geoffrey Keynes states that when in 1922 he published his book with this title, it seemed that one man, with experience such as he had gained during the first World War, could within the compass of one small volume give a satisfactory account of then current knowledge of the subject, but that now, after the second World War, such a project is obviously impossible. He has, therefore, invited seven colleagues, each an acknowledged expert in a different aspect of this enormously expanded subject, to collaborate with him.

Mr. Keynes himself gives an historical survey, which is both scholarly and entertaining. Dr. Bodley Scott deals with clinical indications for and complications of blood transfusion. Dr. H. F. Brewer describes the various blood factors, and the technique he uses or recommends for their identification; he also contributes sections on the organization of a hospital transfusion department and, in conjunction with Mr. F. W. Mills, chairman of the London Voluntary Blood Donors' Association, on the blood donor. This latter section has rather a special appeal to Australians, as the Australian Red Cross Blood Transfusion Service, now the recognized national service for the supply of blood and stored derivatives in this country, was at its inception in a small way in one State in 1929 closely modelled on the London Blood Transfusion Service existing at that time. The technique of blood transfusion in general is dealt with by Mr. Anthony Till, and in infants by Dr. R. W. B. Ellis. Sir Lionel Whitby contributes the section on the storage and preservation of blood and blood derivatives, which in respect of the latter and blood substitutes is amplified by Dr. R. I. N. Greaves.

The authors, however, in spite or perhaps because of their knowledge, are rarely dogmatic, and on several points on which divergence of opinion is justifiable, short but well-balanced analyses of existing evidence are given, together with relevant bibliography; the reader is thus provided with the opportunity and stimulus to form his own opinion.

This wise presentation, therefore, leaves little room for criticism, and even if their own practice differs in some details, those interested in any aspect of blood transfusion will find this compact volume a welcome addition to their libraries as a concise but authoritative expression of the current British concepts and practice in relation to blood transfusion.

[1] "Blood Transfusion", by H. F. Brewer, Richard Ellis, R. I. N. Greaves, Geoffrey Keynes, F. W. Mills, R. Bodley Scott, Anthony Till and Lionel Whitby; edited by Geoffrey Keynes, M.A., M.D., F.R.C.S.; 1949. Bristol: John Wright and Sons, Limited. London: Simpkin Marshall (1941), Limited. 8¼" x 5½", pp. 594, with 109 illustrations, some of them coloured. Price: 52s. 6d.

TECHNIQUE IN THE OPERATING THEATRE.

In "Operating Room Technique" Edythe Alexander has supplied a text-book which will be welcomed by all who are concerned with the administration of operating theatres or whose task it is to train theatre staffs.[1] Several experienced theatre sisters in various large hospitals have given it unqualified praise. It contains all the detail necessary for training nurses and is an excellent reference book for the experienced sister, since the most modern procedures, such as vagotomy, operation for coarctation of the aorta, Monaldi drainage of tuberculous cavities and resection of the œsophagus, are described clearly. Not that it is concerned disproportionately with highly technical matters. Greatest stress is laid on the routine, everyday work of the operating theatre.

It is printed in clear type and illustrated with nearly seven hundred clear illustrations.

SYMPTOMS IN DIAGNOSIS.

It is refreshing to read "Symptoms in Diagnosis" by Meakins and his colleagues.[2] The book has been written with the intention rather to stimulate the reader to analyse such symptoms as the patient presents, than to lead any student or practitioner to an immediate diagnosis. Symptoms lead the patient to seek the doctor's advice, and the proper interpretation of symptoms leads to the application of other forms of investigation, and ultimately to a correct diagnosis. The good physician is the one who uses the least number of laboratory procedures to reach the correct conclusion. The ideal is sympathetically to endeavour to make the patient express himself, and then to assess the factors in their true perspective. The author regards the skin as a very important organ from the point of view of its symptomatology, and allots one-seventh of the whole book to it. He deplores the fact that little energy has been expended in unravelling the mystery of the physiology of the skin when abnormal. The heads of the chapters correspond to the organs from which symptoms arise—the skin, skeletal system, gastro-intestinal system, and so on. The last deals with symptoms in psychiatry. The book is in no way encyclopædic, but sets out the practical application of symptomatology based on the observations of forty years. Two concepts are essential—first the facts as such, second the appreciation of processes, and the application of their diversities to the understanding of the physical and emotional disturbances which plague mankind. In medicine there are no barriers between the "soma" and the "psyche" and their interrelation with the skeletal, visceral, nervous, endocrine

[1] "Operating Room Technique", by Edythe Louise Alexander, R.N.; Second Edition; 1949. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9¾" x 6½", pp. 772, with 668 illustrations. Price: 75s.

[2] "Symptoms in Diagnosis", by Jonathan Campbell Meakins, C.B.E., M.D., D.Sc., LL.D.; Second Edition; 1948. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 9" x 5¾", pp. 462, with 112 illustrations, some of them coloured. Price: 56s.

and other systems. The patient's symptoms are of more importance in the beginning of an investigation than physical signs or laboratory findings. In the opinion of the author, 50% of patients present symptoms only, there are plenty of "complaints" and no physical signs. All medicine is strictly speaking psychosomatic, and in the appropriate chapter, the writer discusses very concisely the evaluation of and the conclusions to be drawn from statements made by patients as to their symptoms. In the chapter on symptoms in psychiatry, the author lays down very emphatically the importance of being alert to the question: "What is the relation between symptom and diagnosis in the field of psychiatry?" The book is written in spirited language, illustrated by diagrams and photographs. Brief case histories are given when necessary to enforce the reasoning. A good index and table of contents make it easy to use the book as a work of reference.

THE PRACTICE OF REFRACTION.

ALTHOUGH the character of Duke-Elder's book on refraction remains unchanged, additions have been made in the fifth edition in a number of sections and the chapter on squints has been reduced.[1] Aniseikonia and the use of the space eikonometer have been given more prominence.

The chapter on heterophoria has been rewritten, the main change being the omission of paralytic squint and curtailment of discussion on orthoptic training. Squints are dealt with only in relation to refractive errors. Additions have been made to the section on spectacles and particularly to that on contact lenses. A chapter has been added on anomalies of convergence. Refractometers and keratometers are more fully described and illustrated. The author's views on myopia have changed as a result of experimental work on the components of the optical system. Although an effort has been made to give the book its first post-war revision there is nothing revolutionary to be found in it.

PATHOLOGY OF THE NERVOUS SYSTEM.

WORKERS AND STUDENTS in neuropathology who have used Biggart's "Pathology of the Nervous System" will welcome a new edition of the work.[2] Thirteen years have elapsed since discerning readers first recognized its straightforward practical presentation of just those aspects of neuropathology of interest to students in medicine desiring a pathological background to neurological reading and clinical work.

During these intervening years, what with the phenomenal increase in neurological studies and magazines, experimental work on animals, brain surgery and the recent accession of importance attached to the diplomas in psychological medicine, a vast amount of new knowledge has accumulated together with a more modern appraisement of older theories. Professor Biggart, practically rewriting every page, has made a commendable effort to embody much of this in his new edition, while increasing its size only by some forty pages. He has, moreover, added forty new illustrations including ten coloured plates. These latter include examples showing how special stains and metallic impregnations reveal specific structure and disease reactions.

The paragraphs on myelinoclasis, from the acute leuco-encephalitis of Weston Hurst, the less acute and diverse forms found in children to the better known chronic disseminated sclerosis types, give a masterly yet simple summation of present-day facts and theories. A good account is also given of the various epidemic encephalitides such as Australian "X" disease and the St. Louis varieties. The lessons of the war and its aftermath—the internment camps—permit a bringing together into a more coherent whole of many odd clinical symptoms and pathological signs together with their vitamin deprivation ætiologies vaguely associated in the past with dietary deficiencies.

The paragraphs on the encephalopathies of lead and alcohol and the various forms of glial reaction in combined sclerosis, Friedreich's ataxia and tabes are suitably written.

Injuries to the nervous system are dealt with from many aspects including discussions on slight cerebral trauma to scar formation in association with epilepsy and cord compressions from *nucleus pulposus* herniations.

The presentation of tumours of the nervous system by dividing them into five main groups after Leonard Cox simplifies a beginner's understanding of a confused and diversified subject, and suitable illustrations add to their clarification. This chapter is rounded off with a discussion on tumours of the *sella turcica* region including the epidermoid group and those of congenital origin.

A chapter on errors in development as well as many helpful allusions throughout the book to accompanying clinical signs makes the use of this presentation of neuropathology a congenial task.

A NEW TEXT-BOOK OF CARDIO-VASCULAR DISEASE.

A NEW text-book of distinguished merit entitled "Heart" and subtitled "A Physiologic and Clinical Study of Cardio-Vascular Diseases", by A. A. Luisada,[1] is stated to have been written for "the large group of physicians who desire to increase their knowledge of heart disease". No doubt most expert cardiologists would count themselves among this group: the book is rather for the student and amateur of cardiology, who should find it a well-stored treasury of the fundamentals of the subject, rich also in material useful for reference. The author was formerly Professor of Medicine at Ferrara, in Italy, and is now an Associate in Medicine at the Beth Israel Hospital, Boston, Massachusetts.

The first chapter of the book is historical and devoted to a chronological list of important advances in cardiology from the description of the *ductus arteriosus* and *foramen ovale* in 1530 to the surgical treatment of coarctation of the aorta in 1945. Other early chapters deal with the development and structure of the cardio-vascular system, with the normal functions of the heart and vessels and with the clinical study of the "cardiac" patient. This last is well done and the senior student and house physician should find it valuable. The tabular classification of heart murmurs published by the American Heart Association is reproduced. In the chapter on the technical study of the patient phono-cardiography is considered in great detail, because of the author's belief that this method will be increasingly important in cardiology: throughout the book the excellent reproductions of phonocardiograms superimposed on electrocardiograms are most helpful. The chapter on the causes and modes of origin of cardio-vascular disease is rather scrappy. The classification of cardiac diseases in future editions could well follow the Standard Classified Nomenclature of Disease, which is not listed in the bibliography, or the recently published classification of the World Health Organization.

The chapters on diseases of the various parts of the circulatory system are all succinctly comprehensive and there is a classical bibliography at the end of each. The paragraphs on the clinical signs of heart disease refer to many hundreds of phenomena which are not commonly described in text-books, some perhaps not of great importance, but mostly of great interest and many probably not widely known outside Europe. The effort syndrome is dealt with, not very convincingly, in a chapter on "borderline syndromes of cardiology". There are chapters on paroxysmal cardio-respiratory attacks, on heart failure, on the cardiac patient as an obstetrical and surgical risk, on drugs, on the management of patients and on medication. At the end of the book is a formulary of one hundred prescriptions—the basis of a sort of cardiological drug-cupboard. Some of the prescriptions are unfamiliar and interesting—for instance, paroxysmal dyspnœa and pulmonary œdema are treated with an intravenous injection of five grains (0·3 gramme) of chloral hydrate with one-sixth of a grain (10 milligrammes) of morphine sulphate. The book is profusely illustrated with diagrams and phonocardiograms and electrocardiograms. The frontispiece is a reproduction of one of the celebrated murals depicting great cardiologists painted by Diego Rivera for the National Institute of Cardiology of Mexico City. Inside the back cover is gummed an inset giving a summary of treatment in cardio-vascular emergencies, each with a reference to the page of the book on which full details will be found. The book's production is a credit to the publishers.

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[1] "The Practice of Refraction", by Sir Stewart Duke-Elder, K.C.V.O., M.A., D.Sc. (St. And.), Ph.D. (London), M.D., F.R.C.S., Hon. D.Sc. (North Western); Fifth Edition; 1949. London: J. and A. Churchill, Limited. 8" x 5¼", pp. 336, with 216 illustrations. Price: 18s.

[2] "Pathology of the Nervous System: A Student's Introduction", by J. H. Biggart, C.B.E., M.D., D.Sc., with a foreword by Professor A. Murray Drennan, M.D., F.R.C.P.E., F.R.S.E.; Second Edition; 1949. Edinburgh: E. and S. Livingstone, Limited. 8¼" x 5¼", pp. 368, with 232 illustrations, some of them coloured. Price: 21s.

[1] "Heart: A Physiologic and Clinical Study of Cardio-Vascular Diseases", by Aldo A. Luisada, M.D., with a foreword by Herrman L. Blumgart; 1948. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 10" x 7", pp. 668, with many illustrations. Price: 75s.

The Medical Journal of Australia

SATURDAY, OCTOBER 8, 1949.

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THE WORLD PROBLEM AND PSYCHIATRY.

As time passes, it is becoming more and more usual to talk about the altered conditions of life and the new and close relationship which nations have with one another. Those who live in the Southern Hemisphere, especially Australians and New Zealanders, are more conscious of change than the peoples of Europe and North America, because, for them, the lessening of distance has been greater. Modern conditions of travel have brought about such a state that the nations of the world live almost in one another's pockets, or in different corners of the same pocket. But the speeding up of travel is, as we all know from our daily lives, but one feature of the altered *tempo*. Whereas in earlier days man walked or even sauntered through life, he now runs or is carried on at a running pace by the hurry of those around him. There is so much to do and so little time to do it in, that it has been said with truth that if one does not overwork, one underworks. It is not only what a man does by himself or for himself that is part of the rush and scurry. Men work in groups, large and small, seeking their own ends and caring little for the fate of those who differ from them. There has been bred what is known as a war of nerves, and those who wage it use fear as a vehicle, and rely on speed or the threat of speed to achieve success. When we try to discover what has brought the world to its present convulsive state it is not sufficient to look at what is going on around us; we must look at man himself. Man has changed; he has discarded old ideas and forsaken some of his ideals. The two world wars are blamed—war, we are told, is primitive, cruel and brutal, and brings out all that is worst in man, and man, having fallen from an estate which may or may not have been high, has gone on his way at a lower level than he chose before. But war is an effect and not a cause—action and reaction do occur, but wars take place because man is what he is. What the first and second world wars did was to quicken the disintegrating process and bring it to the surface. It was something like a progressive septicæmia which takes on a new virulence and manifests itself by suppurative pyæmic foci in the surface of the body and in the vital organs. This simile is useful if we look for a possible remedy to the ills of humanity.

Practitioners of medicine are specially qualified to think about this subject because they deal with individuals and their ambit includes everything that the individual experiences and does. Since ideas and ideals are largely concerned it has often been held that the aid of psychiatrists should be invoked, though in fact any medical practitioners of discernment, who have a philosophical outlook, should be able to make contributions. Reference to this subject has been prompted by an address recently delivered by Professor Thomas A. C. Rennie on the subject of "Psychiatry in Medicine and Society".[1] Rennie referred to the widespread incidence of neurosis and to the need for diagnosis and treatment by psychiatrists of the problems of society. He holds that, even if the psychiatrist is not interested in such problems, he is compelled to give consideration to them because of the appeals for help that come from such divergent persons as medical practitioners, psychologists, social workers, educators, the clergy, employers, labour leaders, statesmen and others. Whether appeals of this kind are common in Australia. is open to doubt. The general impression seems to be that the advice of psychiatrists is not sought so often as it should be. However, whether this impression is correct or not, there is no doubt that preventive psychiatry is as necessary to the community as preventive medicine. There does not seem to be sufficient justification for the naming of "social psychiatry" as a new science—this is what Rennie suggests. Everyone engaged in the practice of social medicine realizes that any success that he achieves depends to a large extent on the mental atmosphere which prevails in his particular *milieu* or which he is able to produce. Rennie refers to three major influences which have been operating to promote mental health and morale in industry. First of all "in the business of war it has been discovered that certain kinds of work, of risk, of responsibility and of discipline improve men's spirits and that other kinds break them". The second point is that besides selection and training for the job, the armed forces developed methods of building morale; "particular consideration was shown for each man's personal welfare and value in cooperative effort, and emphasis was placed on teamwork and social solidarity". In the third place, "the concept that each man's potential in production is much higher than has generally been realized and that men are capable of great accomplishment and discipline when they share closely in a common enterprise under leaders whom they trust and admire proved its practical truth during the war". Rennie thinks that it is time that this concept was applied to industry. Many people will agree with him, but to think that such an application is likely to be effected in the near future is to entertain a pious hope and to be entirely divorced from reality. Rennie referred at length to education and made what we may call a Utopian statement that, at all levels of school, guidance and clinical work are needed "to restore to health and social effectiveness those children and youths whose growth, integration, or socialization is being blocked by inner conflicts or environmental stresses".

[1] "Psychiatry in Medicine and Society", The S. Weir Mitchell Oration XI, delivered on January 5, 1949. *Transactions and Studies of the College of Physicians of Philadelphia*, April, 1949.

There is no doubt that the two spheres of activity, industry and education, as well as the third mentioned by Rennie, that of religion and faith, are of the greatest significance in what we may call the much needed world therapy. Rennie's address shows also that much more than abstract thinking and surface knowledge is needed. He states that if our "free enterprise system" is to function adequately, private business and industry must do much more to stabilize employment and guarantee economic security, and labour groups must develop real leadership and take steps to assure full productivity. He goes on to remark that it is necessary for both groups "to take aggressive steps to achieve and maintain full employment, that is, to give everyone the opportunity for steady, gainful, satisfying employment on a year-round basis". The truth is that a system of free enterprise and of full, steady, gainful and satisfying employment cannot coexist. Full employment necessarily includes an element of compulsion if a system is to function adequately and the system will not then be free. And human beings will need to change a good deal if full employment in a properly functioning system is to be satisfying. This serves to emphasize the difficulty of the whole problem. There is some hope from the fact that earnest minds are trying to find a solution. They may not be many in comparison with the mass of people who have to be influenced, but they can have a far-reaching effect. There is no reason to despair, for we can always think of the little "leaven" that leavens "the whole lump". Berdyaev has written that there are two distinctive features in the new era of the modern world. On the one hand there is the extraordinarily rapid almost fantastic development of techniques, the domination of man over the elemental forces of nature, his penetration into cosmic life. On the other hand there is the active participation in history of enormous masses of humanity. He holds that the agonizing character of our times results from the failure of the spiritual growth of man to correspond to these dynamic processes. Who shall contend that he is wrong? For everyone the problem is at the onset a personal one.

Current Comment.

PURPURA DUE TO HYPERSENSITIVITY.

DRUG SENSITIVITY is one of the prices paid for the help given by some of the modern therapeutic agents. Thrombocytopenic purpura is not a common condition, but it is not likely to be overlooked, and when it occurs during the administration of a drug the relation between the two is immediately suggested. J. F. Ackroyd has published a study of the pathogenesis of this blood disorder due to one member of a group of hypnotics that are in common use.[1] The drugs chiefly responsible for this type of sensitivity are the arsenobenzols, the sulphonamides and "Sedormid", and in addition there is an imposing list of other substances which have been blamed. "Sedormid" is the commercial name for one of the open chain ureide drugs used as hypnotics; others often used are "Adalin" and "Bromural". It is curious that "Sedormid" is the only member of this group which has caused this form of sensitivity in spite of the strong family resemblance between the structural formulæ of all drugs of this type. Experiments have not even demonstrated any tendency to purpura from the other group members after an episode had occurred due to "Sedormid". This specificity is only relative, as will be shown later. Ackroyd rightly points out that circumstantial evidence of sensitivity following the taking of certain food or a certain drug may be highly suggestive, but is not convincing unless a similar reaction can be produced by readministration after recovery. The first case of this variety of toxic purpura was reported in 1933, and since that date over forty cases had been described by 1940, a figure which has been greatly increased since. Purpura due to this cause usually occurs only after the patient has been taking the drug over a considerable period, of weeks, months or even years, and has often appeared after an intermission. In almost all the published accounts the purpura has been of the thrombocytopenic type, and in one or two instances the hypersensitivity evoked by one drug was afterwards produced by another and quite different substance. This is a familiar sort of "overflow" reaction seen in hypersensitive episodes in other branches of medicine. Hypersensitivity once produced may last even for years, but in some instances it has disappeared quickly. Therefore it is interesting and important to know whether skin testing will reveal this specific state. Some of the published articles claim that skin tests with drugs responsible for causing purpura fail to demonstrate a local reaction, but Ackroyd has shown that local purpura can be obtained by a patch test, particularly when propylene glycol is used as a solvent. Full investigation of the processes at work in causing purpura has been made by the author. The results answer a number of questions. The amount of the drug which may evoke a response is, as one would expect, extremely small in some persons, once made sensitive. Thrombocytopenia is not a necessity in the production of purpura, in spite of its almost constant presence in this condition, and the connexion between the two is not quite clear. Many hold that the low platelet counts are related to efforts on the part of these blood elements to repair the capillary damage which is a significant feature. Ackroyd concludes in this instance that two separate conditions exist, a capillary defect and a deficiency in the number of circulating platelets. As the available supply of the latter falls, so the tendency to bleed from the damaged capillaries increases. Various other phenomena have been observed. The drug caused agglutination *in vitro* of platelets in a few cases, and also reduced clot retraction, but none in controls. Attempts to transfer sensitivity to other subjects were unsuccessful. It has been remarked already that other members of this group of drugs apparently do not produce sensitivity manifest as a purpuric reaction, but it is of interest to learn that reduced clot retraction has been produced in patients who have had purpura due to "Sedormid". Obviously there is some capacity to affect blood function in certain persons which is common in some degree to all these ureide drugs. Ackroyd has found that the application of tests on the behaviour of the skin, on blood clot and on the platelets is useful in differential diagnosis, though obviously all of these could be carried out only in fully equipped laboratories. The patch test is, of course, easily applied anywhere.

This study is interesting as a detailed account of a manifestation of sensitivity which may not be generally known. It reinforces the lesson that drug reactions are now an important part of the field of modern clinical medicine.

[1] *Clinical Science*, Volume VII, Numbers 3 and 4, 1949.

FURTHER REPORTS ON VITAMIN B_{12}.

EARLY WORK on vitamin B_{12} and its use in the treatment of pernicious anæmia was mentioned in these columns on February 12, 1949. Despite the fact that supplies of this potent substance are still small, the literature on its use is gradually mounting. The full composition of vitamin B_{12} is not yet determined, but it is known that its molecule is built around a single cobalt atom and contains also phosphorus and nitrogen. Reports indicate that it is effective in inducing hæmatological remissions in persons with pernicious anæmia, non-tropical sprue, nutritional macrocytic anæmia and tropical sprue, and as far as can be judged from a limited period of observation it has

produced encouraging effects in cases of subacute combined degeneration of the spinal cord accompanying pernicious anæmia. Two of the more recently published papers illustrate the results now being obtained.

R. West and E. H. Reisner[1] report the results of parenteral administration of crystalline vitamin B_{12} to eleven patients with Addisonian pernicious anæmia. All had the classical form of the anæmia with achlorhydria after histamine administration, a normal gastro-intestinal tract according to X-ray examination, a typical blood picture and a megaloblastic bone-marrow smear. In all cases hæmatological improvement occurred, blood counts rising to normal levels when weekly doses of 25 microgrammes or less were injected. The minimal effective dose was found to be one microgramme (or slightly less) a day given intramuscularly. Five patients with spinal cord lesions have experienced varying degrees of improvement; none has become worse, as has happened at times in treatment with folic acid, and all are walking readily today.

The oral administration of vitamin B_{12} is the subject of a report by T. D. Spies *et alii*.[2] A total of 49 patients (16 with pernicious anæmia, 17 with nutritional macrocytic anæmia, 14 with tropical sprue and two with non-tropical sprue) were given vitamin B_{12} by mouth. The general conclusion was that, given in this way in adequate amounts, the vitamin is often efficacious, but it is less so per unit of weight than when given parenterally. The minimal, maximal and optimal doses vary from patient to patient and from time to time in the same patient, and so must be determined in the individual case. On the whole, most patients respond slowly when vitamin B_{12} is given by mouth in an amount 30 to 60 times by weight that required for parenteral therapy. It is important to note also that, as soon as possible, the patient should have a diet that supplies adequate Calories and a liberal amount of protein of high biological value. Spies *et alii* consider that, irrespective of age or any other condition, vitamin B_{12} should always be given parenterally when the patient has severe cardiac failure, severe neural degeneration, or a severe alimentary disturbance, and for most extremely ill patients the initial treatment at least should be parenteral. If patients are later found who react severely to injections of vitamin B_{12}, as some do to liver extract, it will be comforting to know that oral therapy is often effective. Meantime parenteral therapy appears to be more reliable and efficient and certainly more economical of a rare and costly substance.

ALLERGY AND THE COMMON COLD.

ONE of the favourite jests levelled at the medical profession is that, in spite of the advances made in pure and applied science, it cannot yet control the common cold. Of course, there is a fallacy in thinking that because something is so common as to be of daily experience it is necessarily easy to understand or can be dealt with simply. To begin with, it is doubtful if all people who claim to have a "cold" really have the same complaint. Perhaps it might be worth while to lay down criteria for the diagnosis, though this would be difficult and might need the skill of a constitutional lawyer as well as the controlled doubts of the laboratory worker. Still, if we assume that we know what is meant by the common cold, whether it is complicated by troublesome extensions to the paranasal sinuses or not, it is interesting to traverse the subject again and see what the inquiring rhinologist has to suggest. Noah Fox and George Livingston have collected a quantity of references from the profuse literature, and after examining the work and ideas of others, have tried to assess the connexion between allergy and the familiar type of rhinitis believed to be due to an infective agent, presumably a virus.[3] They comment on the almost universal belief that these infections are in some way due to a lowered resistance caused by chilling. Some workers have shown that persons exposed to cutaneous chilling have vasoconstriction in the nasal mucosa, affecting the surface vessels and lowering the surface temperature. Others have not found convincing changes. Sufferers from a head cold have been shown to possess a delayed reaction to the stimulus of cold. But no sure link has been proved to exist between a faulty functioning of the heat regulating mechanism of the body and the multiplication of a specific virus. In fact where the infective common cold has been experimentally transferred from one person to another no chilling mechanism has been operative, though this does not dispose of the possibility that the latter may predispose to infection in some manner not understood.

The authors explore also the literature about climate, especially cold climates in places where isolated communities live. Here it has been found that the important factor is the introduction of the infection from outside, after which every person in the community contracts the disease. This phenomenon has often been observed, the interesting feature being the previous freedom from such infections in spite of rigorous conditions, such as exist, for example, in polar expeditions. So well known an authority as Leonard Hill stated that exposure even to extremes of cold does not *per se* increase the liability to contract infective rhinitis or other respiratory infections. A number of years ago it was a therapeutic fashion to nurse patients with pneumonia on a balcony; it never did harm, and appeared to do good. Analyses have also been made of communities like schools, in order to expose any relationship between colds and metereological conditions. Some have concluded that the steepness of gradient of the fall of temperature is related to outbreaks of colds. Rather more scientific are the attempts to relate physical exertion and fatigue to the infection. By estimating the capacity to withstand fatigue in terms of oxygen consumption an attempt has also been made to relate the response to exercise to the liability to "catch cold". Locke, by these and other tests establishing a ventilation quotient for the individual, claimed that he could distinguish the more from the less susceptible, taking care to exclude persons with a frank allergy.

Other attempts have been made to establish a constitutional factor, and as they rest on an experimental basis they suggest that such factor or factors are a reality. Fox and Livingston seek to show that this factor lies in the allergic diathesis. Of course, there is much presumptive evidence in favour of this, but we have to be careful that the "colds" that these people exhibit are truly infective, and not merely the symptoms of a transient vasomotor rhinitis. The authors quote from Coca and others who have worked in the field of allergy, and on this basis and their own observations, suggest that a sensitivity to a particular protein exists, which activation of a present virus brings to light, aided by the systemic reaction produced in a cold-sensitive person by exposure to cold. They present figures showing that out of some 3000 persons subject to the common cold, the majority have a history of some other type of allergy, either of clinical or subclinical kind, very few are quite free from a family history of allergy, and all have hyperplastic disease of the upper respiratory tract. The last condition is responsible for a further liability to complicating sinusitis.

An interesting observation was made by Fox and Livingston in connexion with the assumption that such people often harbour bacteria in their upper air passages. They made biopsies of the antral mucosa of 25 allergic patients, after failing to grow organisms from washings of the maxillary sinuses, and from these tissues never failed to grow many different types of bacteria of the type found in nasal infections. Finally the authors conclude that there is no evidence that the popular notion is correct that exposure to various external factors of environment and exertion predispose to the common cold, but think that the allergic factor is significant in facilitating the activation of infective agents already present, or introduced from without. The hypothesis has much to commend it, but perhaps we may be wary of labelling patients as presenting a subclinical type of allergy. This idea, like the name of the common cold, perhaps requires some careful definition.

[1] *The American Journal of Medicine*, May, 1949.
[2] *The Lancet*, September 10, 1949.
[3] *Archives of Otolaryngology*, June, 1949.

Abstracts from Medical Literature.

SURGERY.

Carcinoma of the Pancreas.

H. K. Gray (*Archives of Surgery*, December, 1948) discusses carcinoma of the pancreas as part of a symposium on cancer. He states that the past fifteen years have produced a changed situation in the attitude of the surgeon to cancer of the pancreas, and there is now a willingness on the part of many surgeons to perform partial and even total pancreatectomy without fear of imposing undue risk. The author discusses certain pathological features of the two main types of pancreatic carcinoma, quoting Ewing. It appears that jaundice will be present practically always when the lesion involves the head of the pancreas. The jaundice is usually intense and constant, and when associated with a distended gall-bladder suggests obstructive jaundice due to carcinoma of the head of the pancreas. Cachexia and loss of weight are usually symptoms of advanced carcinoma and in most instances will be present in a patient in whom the malignant condition has progressed to the point at which surgical excision is no longer possible. The value of laboratory tests is discussed, and a table is presented indicating factors in the differential diagnosis of hepatogenous jaundice and obstructive jaundice due to carcinoma of the head of the pancreas. The pre-operative preparation is detailed and some discussion is given as to the method of removal in stages.

Treatment of Acute Anuria.

A. Fields *et alii* (*Annals of Surgery*, April, 1949) have reviewed the treatment of acute anuria. A urinary output of less than 50 millilitres per day was regarded as anuria. They treated six patients with potentially reversible tubular renal lesions and one with acute glomerulonephritis. Three patients survived. The patients were treated by peritoneal lavage of a modified Tyrode's solution introduced through a de Pezzer catheter in the upper part of the abdomen at the rate of one litre every forty-five minutes and aspirated through a Chaffin tube in the pelvis. Five of the patients treated were œdematous when first seen. The authors point out that if any sodium is given it will be retained and water with it. They state that there is no evidence that alkalinization following a transfusion reaction or sulphonamide injury reverses the damage done. The forcing of fluids in anuria does not raise the glomerular filtration pressure or break the "tubular block". Again, even without intravenous administration of fluids and sodium, anuric patients tend to develop spontaneously pulmonary œdema. With the onset of diuresis, however, rapid loss of electrolytes may occur. If shock and anuria should coexist, then the underlying causes of the shock must be treated vigorously to restore and maintain normal circulating blood volume and electrolyte levels. If, however, the patient is still anuric after twenty-four to forty-eight hours the forcing of fluids and sodium by the intravenous route may lead to overloading of the circulation. Prolonged use of intraperitoneal lavage will lead to the absorption of appreciable amounts of fluid from the peritoneum. Hypertonic fluids are contraindicated at all times because of the risk of pulmonary œdema. During the course of the anuria the electrolyte concentrations may vary—hence biochemical control is necessary; if this is impossible some of the effects may be gauged from an electrocardiogram. The chief value of intraperitoneal lavage is in cases of hyperpotassæmia, electrolyte imbalance and severe azotæmia. Various agents were used in an effort to control vasospasm in the kidney without demonstrable benefit. The survey showed that intraperitoneal lavage was of value in removing substantial amounts of nitrogenous waste products, provided an indirect means for supplying glucose was helpful in adjusting a disturbed electrolyte pattern, especially in regard to potassium. The disadvantages were the need for constant and expert supervision and nursing, contamination of the peritoneum and the absorption of fluid from the peritoneal cavity if hypertonic fluid was given simultaneously by the intravenous route.

Treatment of Carbuncles by the Local Injection of Penicillin.

Thomas H. Bate (*Annals of Surgery*, April, 1949) reports the treatment of carbuncles, all of large size, in twenty cases. A solution was used containing 100,000 units of penicillin to each millilitre of 2% "Novocain" solution freshly mixed; five to twenty millilitres were usually sufficient. A very fine hypodermic needle was used with a lock type of syringe. The skin just beyond the indurated area was carefully cleaned. A small weal was made in the skin, and the deeper tissues were injected. Three to five points were used to surround the carbuncle completely. The solution was not injected into the carbuncle. Hot packs are recommended. There was immediate relief from pain. The drainage was usually profuse on the second day and persisted for two or three days. Epithelialization was rapid. The scar was thin and white and not adherent to the surrounding tissue. The induration subsided over two to four weeks. The average number of days lost from work was 8·6.

Strangulation of Small Intestine and Viability.

J. Gaster, H. A. Davis, P. A. Pritel and R. L. Marsh (*Archives of Surgery*, March, 1949) have conducted a series of experiments on rabbits in order to determine what length of small intestine can be devascularized and retain viability. The devascularization was effected by ligating vessels in the mesentery of the ileum, and tests were done with lengths of 5·0, 6·0, 7·0, 7·5, 8·5, 10·0 and 13·0 centimetres. The only blood coming into the devascularized area at the end of the operation was through the fine intramural vessels at each end of the ligated segment. The sudden removal of the blood supply of five, six and seven centimetre lengths of small intestine was compatible with life in the rabbit. When larger segments were devascularized, gangrene, perforations, peritonitis and death formed the usual course of events. When five centimetres of intestine were devascularized the intestine was able to maintain viability by the entry of blood from the intramural vessels. When longer areas were devascularized, this was insufficient to maintain viability and the blood supply was seen to come from adherent adjacent loops of intestine, from ingrowth of new vessels into the healed mesentery, from the omentum and from vascularized adhesions from parietal peritoneum. The experiments closely reproduce the condition that exists in acute mesenteric thrombosis and embolism, in strangulated intestinal obstruction, and in stab wounds of the mesentery.

Thyreo-Glossal Cysts and Sinuses.

S. F. Marshall and W. F. Becker (*Annals of Surgery*, May, 1949) report a group of 348 cases of thyreo-glossal cysts and sinuses treated surgically. They discuss briefly the anatomy and embryology of the thyreo-glossal tract and its close association with the hyoid bone. Thyreo-glossal fistula or sinus is very rarely a congenital condition, and patients with thyreo-glossal cysts and sinuses may present for treatment at any age. In the largest group of the series, however, the cysts occurred before the age of forty-one years. The authors state that these embryonic tracts will remain quiescent in the neck for many years and then suddenly give evidence of their presence by forming a cyst. This development of fluid may be evidence of irritative phenomena, probably inflammatory, which may well account for the sudden development of a cyst. The diagnosis of thyreo-glossal cyst is not difficult, and the successful treatment, as Sistrunk pointed out in 1920, is removal of every trace of the thyreo-glossal tract up to the *foramen caecum* at the base of the tongue. Details of the operation generally associated with the name of Sistrunk are given. In a study of 310 of the 348 cases, the authors found recurrences in four only, and in these cases the hyoid bone and the tract above were not removed.

Rationale of Therapy in Acute Vascular Occlusion.

W. B. Martin, H. Laufman and S. W. Tuell (*Annals of Surgery*, April, 1949) have studied the effects of commonly used agents on the calibre of mesenteric vessels after occlusion of a main vessel. When the superior mesenteric artery was clamped, both the small artery and small vein under observation diminished in calibre. On release of the occlusion the artery remained in moderate spasm before returning to its original calibre. After clamping of the superior mesenteric vein the small veins became dilated, whilst the small arteries showed a marked diminution of calibre. On release of the occlusion the same temporary residual vasospasm was noted. As the artery returned to its normal calibre the engorged vein also approached normal. The afferent and efferent sympathetic innervation of artery and vein was largely responsible for the patterns of response following occlusion. The pressure gradient is important only when the spastic impulses are weak enough to be overcome by the intravascular pressure. Oxygen therapy had no effect on vessel calibre. Papaverine hydrochloride was of value in releasing some reflex arterial spasm in venous occlusion if used before thrombosis occurred. In arterial occlusion it was of value only when collateral arteries existed above the

occlusion. If not injected very slowly it may cause temporary stimulation of respiration and precipitous drops in blood pressure. Tetraethylammonium chloride in non-shock-producing doses was able to counteract vasospasm in venous occlusion in only half the cases and in acute arterial occlusion was without value. Heparin and dicoumarol prevented thrombus formation in the involved vessels. They did not influence the formation of sludge or the calibre of the vessels observed. Regional sympathetic denervation eradicated the pattern of small vessel spasm to an extent unequalled by the generalized vasodilators employed; however, once an occlusion was released, such drugs were usually able to counteract residual vasospasm. Sludge formation usually appeared within ten to twenty minutes after a venous occlusion, and thrombus formation was noted in some small vessels about thirty minutes after the formation of sludge. The authors conclude that the importance of early anticoagulant therapy in the occlusive vascular states is obvious.

Hiatus Hernia.

G. G. RICHARDS AND K. A. CROCKETT (*Archives of Surgery*, April, 1949) state that they have found more patients with hiatus hernia in the last eighteen months than in the previous thirty years. Portion of the stomach herniates through the œsophageal opening of the diaphragm. The condition is not at all rare, and is frequently overlooked, the patients being treated for peptic ulcers, disease of the gall-bladder or coronary heart disease. Not infrequently the same patient may have any of these conditions along with the hiatus hernia. The condition occurs most frequently after the age of fifty years, and reports indicate that it is more frequent in females than in males. The commonest symptom is pain, usually under the lower half of the sternum or in the epigastrium. It may be referred to the back or up into the left shoulder or arm. It occurs most frequently after heavy meals, especially if they are followed by stooping, lifting, lying down or rising up in bed, or by anything which increases intraabdominal pressure. Dysphagia may be the first symptom. Hot or cold fluids or foods, as well as roughage, may cause painful swallowing. A correct diagnosis can be made only by careful X-ray examination.

Distension of the Subarachnoid Space in Infants.

C. BAGLEY, JUNIOR, R. K. THOMPSON AND R. M. N. CROSBY (*Annals of Surgery*, May, 1949) present a clinical syndrome resulting from the introduction of blood into the subarachnoid space. They avoid the use of the term hydrocephalus, as this term is associated with a feeling of hopelessness in both doctors and patients. This syndrome is characterized by increased intracranial pressure, evidence of meningo-cerebral irritation and distended subarachnoid space as demonstrated by pneumoencephalography. It is to be differentiated from ordinary hydrocephalus, which is characterized by dilated ventricles, and from subdural hæmatoma. The authors maintain that infants with enlarging heads should be subjected to air studies to determine if the condition described is present, since response to surgical therapy appears promising. The authors quote the follow-up records in several cases originally reported by Bagley in 1928. They believe the condition to be due to blockage of the absorption channels of the cerebro-spinal fluid with blood and secondary meningeal hyperplasia with increased intracranial pressure. In turn, this is augmented by increased osmotic pressure of the abnormal spinal fluid, which further retards normal absorption. These changes produce increased intracranial pressure with reduction in effective hydrostatic pressure and slowed cerebral blood flow. Drainage of the subarachnoid space relieves the altered osmotic pressure, reduces intracranial pressure and allows vascular dynamics to return to normal.

The Diagnosis of Lesions of the Breast.

W. T. FITTS AND J. G. DONALD (*Surgery*, March, 1949) discuss 250 cases of lesions of the breast referred to a surgical service. Of the patients, 58% (with an average age of forty years) had chronic interstitial mastitis, 19·2% (average age fifty years) had carcinoma of the breast, and 8·4% (average age thirty years) had a fibroadenoma; 48% of those with carcinoma were proved to have axillary metastases. Most of the cancers were described as hard and most of the benign lumps as firm. One-half of the cancers were not attached to the skin. More than half of the fibroadenomata were "slippable". The cancers and the fibroadenomata were characteristically non-tender. The pre-operative diagnosis was about 75% right. The diagnosis at the time of operation, based on macroscopic or frozen section examination, was almost always right. Axillary metastases were not recognized pre-operatively in one-half of the cases in which they occurred. Among 22 patients thought to have metastases pre-operatively, in only 11 cases was the opinion confirmed microscopically. In 170 cases a "dominant" lump was found. The authors state that the recognition of such a dominant lump is of more importance than the actual pathological nature of the mass. Dominant lumps must be explored surgically. Aspiration of cysts is not recommended for general adoption.

Chemosurgical Treatment of Parotid Gland Tumours.

F. E. MOHS (*Annals of Surgery*, March, 1949) reports that in a determinate series of ten patients with carcinoma of the parotid gland treated by means of chemosurgery, six were free from cancer for five years or more. He states that this is almost twice as good as the results in comparable series treated by various authors by means of surgery with or without radiation therapy. A keratolytic, dichloracetic acid, was applied to the skin over the tumour till the skin whitened. Then a layer, three millimetres thick, of "zinc fixative paste" was placed over the tumour and covered with a layer of "Vaseline" gauze. After twenty-four hours the painless excision of blocks of tissue, about one centimetre in depth, was possible. Further applications were then made and the procedure was repeated. When the margin of the obviously neoplastic zone was reached histological study was made to determine directions of extension. These were plotted on the area and a specific application of the paste was made to these regions. Extensions were found along the perineural lymphatics about the auriculo-temporal nerve and along the perimysium of the stylo-hyoid muscle. Thus microscopic control not only served the demands of conservatism—enabling facial nerve function to be preserved to a varying extent—but also ensured radical extirpation. When the infiltration was thought to be deep, preliminary ligation of the external carotid artery was carried out. Five days after a cancer-free plane had been reached, the final layer of fixed tissue was removed and the wound left open. The wounds healed well. Such salivary fistulæ as persisted responded well to the local use of the zinc chloride paste. The method seemed particularly useful in recurrent cases.

Exposure of the Cardiac Septa.

F. D. DODDRILL (*The Journal of Thoracic Surgery*, June, 1949) has used experimentally a method by which a chamber of the heart, either the right atrium or the right ventricle, is opened, the septum exposed for short intervals and the incision closed. A clamp with a ring on the end is used to bring the lateral walls of the atrium in apposition to the septum. The incision is made within the ring, which excludes the circulation from this area. Portions of the atrial septum have been incised and the defect closed. The exposure of the ventricular septum is more difficult, but has been accomplished with the same instrument.

Testosterone Propionate and Breast Carcinoma.

J. R. WATSON AND G. H. PETTERMAN (*Surgery, Gynecology and Obstetrics*, June, 1949) review the published series of cases of carcinoma of the breast in which treatment was with androgens. Because of the conflicting claims in such cases they undertook the treatment in seven cases themselves. Testosterone propionate was given intramuscularly in doses of 200 to 250 milligrammes twice a week for a total of 3000 milligrammes. It was then reduced to 50 milligrammes every other week and continued for some time. Where possible cutaneous or lymph-node metastases were removed for examination after the administration of at least 2000 milligrammes of testosterone. All patients noted an increase in the sense of well-being, which appeared two to three weeks after the treatment was begun. It was greatest in the most debilitated and lasted from two to five months. There were no adverse effects and no evidence of hirsutism. No evidence was obtained in this series of seven cases to indicate that testosterone propionate had any specific effect on advanced carcinoma of the breast, that it altered the course of the disease, or that it resulted in any improvement in the survival rates obtained by the more commonly accepted forms of therapy. The pain of bone metastases was relieved in two patients who had such lesions when treatment started, while union occurred in the one patient with a pathological fracture. One patient developed a painful bone metastasis whilst under treatment. There is evidence to show that systemic improvement, relief from pain and calcification of bone metastases are due to the anabolic effects of the drug on the entire body rather than any specific effect on tumour cells.

British Medical Association News.

SCIENTIFIC.

A meeting of the New South Wales Branch of the British Medical Association was held at the Women's Hospital, Crown Street, Sydney, on July 21, 1949. The meeting took the form of a series of short papers and clinical demonstrations by members of the honorary medical staff of the hospital.

Intraligamentary Lateral Cervical Fibroid Tumour.

Dr. R. B. C. Stevenson discussed the case of a married woman patient, aged thirty-seven years, on whom he had performed total hysterectomy together with the enucleation of a large intraligamentary lateral cervical fibroid tumour, measuring ten centimetres in diameter. The case was discussed because of two interesting features. Firstly, the rate of growth of the fibroid tumour had been observed during a period of five years, and secondly, the rapid enlargement and subsequent partial involution of the tumour had been observed during the course of a full-time successful pregnancy. When first noted the tumour was 2·5 centimetres long and 1·5 centimetres wide, and was jutting out into the base of the right broad ligament. It was discovered during the course of a routine post-natal examination *per vaginam* following the natural birth of the patient's first baby six weeks previously. The tumour slowly increased in size during the next five years, but until a few weeks before operation there were no symptoms referable to its presence. Three years after the birth of the first baby, the patient became pregnant again. When the pregnancy had advanced to ten weeks, the fibroid tumour in the cervix was found to be about six centimetres in diameter. At the twenty-eighth week of pregnancy the tumour was eight centimetres in diameter and was obstructing the birth canal. At the fortieth week, Cæsarean section of election was performed. At that time the tumour was almost completely filling the *pelvis minor*, and numerous large tortuous blood vessels were noted coursing over it. As it was attached very low down to the side of the cervix, it was impossible to remove it without removing the uterus. In view of the extreme vascularity already mentioned, it was decided to sterilize the patient and wait for involution to occur before attempting hysterectomy. When the baby was two months old the tumour had involuted to six centimetres in diameter and was symptomless. About fifteen months later the patient complained of aching in the right leg, a sense of pressure in the lower part of the abdomen, and increasing constipation. Operative treatment was deemed advisable, and Dr. Stevenson performed a hysterectomy a few weeks later. At operation the fibroid tumour was found to be ten centimetres in diameter; it was intraligamentary, and was attached to the lateral side of the *cervix uteri* between the ureter, which it displaced laterally, and the uterine artery, which it displaced upwards. The uterus with the tumour attached was exhibited, and sections cut from the tumour were shown on the screen by means of the micro-projector.

Dr. Murray Moyes, the pathologist at the hospital, demonstrated the slides, which revealed the following features. The tumour was generally very cellular but innocent, consisting of interlacing fasciculi of plain muscle fibres with numerous thin-walled blood vessels between and amongst the muscle bundles and many fat cells, generally occurring singly, but occasionally in pairs or small groups. It was pointed out that fat in myomata was uncommon and that the following three theories as to histogenesis had been put forward. (i) Metaplasia had taken place of muscle cells into fat cells; that theory lacked evidence and was not widely accepted. (ii) It was a sequel to degeneration, particularly hyaline; again evidence was lacking for that theory and in the specimen under discussion there was no evidence of degeneration. (iii) In reality it was a mixed tumour with origin from multipotential cells. That was a logical explanation more in keeping with the current conception of the genesis of tumours. There was no evidence that the pregnancy was in any way responsible for the presence of the fat cells.

Dr. Stevenson also exhibited X-ray negatives showing the presence of intrauterine fœtal achondroplasia. The mother had an ante-partum hæmorrhage, and the baby was fortunately stillborn.

The Treatment of Abortion with Stilbœstrol Instead of Progesterone.

Dr. Alan Grant discussed the treatment of abortion with stilbœstrol instead of progesterone. He said that there were many causes of abortion and therefore there must be more than one treatment. He referred at the moment only to that group in which the ætiology was thought to be endocrine, and in particular to the group in which the endometrial biopsy showed a hyposecretory or subsecretory histological picture. The patients in that group were treated with stilbœstrol instead of progesterone. That method of treatment was introduced by Karnacky, of the United States of America, in 1942, and had since been expounded by Smith and Smith, also of the United States. The basis of the treatment was the observation that the administration of stilbœstrol during pregnancy resulted in an increased blood titre of progesterone and not of œstrogens only. Stilbœstrol administered during pregnancy might therefore be referred to as "the poor woman's progesterone". It was important to realize that stilbœstrol was not given because it was an œstrogen, but because it increased the blood titre of progesterone. When stilbœstrol was given as a prophylactic the dose should be not less than 10 milligrammes *per diem*. For threatened abortion 50 milligrammes or thereabouts should be given at once and about 25 milligrammes every hour until the bleeding stopped. A very complicated dosage table had been recommended by Smith and Smith. Up to 300 milligrammes had been given in one day without any ill effects.

Dr. Grant said that in assessing the result of any form of treatment it was necessary to have some yardstick or standard. He then showed a table of results of the spontaneous cure rate of patients who had suffered from two and from three previous abortions. One table was from the published figures of Malpas, of England, and one table was from those of Eastman, of America. He then showed a third table indicating the results of treatment by stilbœstrol at the Women's Hospital, Sydney. The figures showed that the administration of the drug had caused a 10% improvement in the group of patients with two previous successive abortions, and a 100% improvement in the group of patients who had previously suffered from three successive spontaneous abortions. Dr. Grant recommended it to the medical profession as worthy of an extended clinical trial. He said in conclusion that the work had been done with the aid of a grant from the National Health and Medical Research Council of Australia.

Ovarian Cysts Associated with Pregnancy.

Dr. S. Devenish Meares discussed the treatment of ovarian cysts in association with pregnancy, reviewed twenty consecutive cases from the hospital records, and referred to three cases in which treatment had been successful during the past six months. He said that ovarian cysts were found infrequently during pregnancy, perhaps once in 2000 cases. Most often the tumours were symptomless, being found on routine antenatal examination, usually before the third month. About half were palpated in the abdomen, having risen there owing to their size or owing to the growth of the uterus during pregnancy. In that situation they were often difficult to feel, being soft, lying in a gutter to one side of the vertebral column, having a long pedicle and so being very mobile, and having their lower poles too high to be felt *per vaginam*. Torsion of the pedicle was the main complication, being twice as common during pregnancy. The differential diagnosis was from cystic swellings of other abdominal organs, ectopic gestation, and retroverted gravid uterus. If they were treated conservatively, abortion occurred in 25% to 30% of cases.

Dr. Meares went on to say that operation should be undertaken as soon as the cyst was found. The operation of choice was ovarian cystectomy with conservation of all ovarian tissue. Ovarian cystectomy was preferred to oophorectomy, for the patients were young—the average age was twenty-four years—the tumours were benign and in 8% of cases they were bilateral. When oophorectomy was performed in young patients subsequent disease of the other ovary might lead to an early menopause with incapacity. Of the three patients treated by Dr. Meares, the first, aged twenty-two years, had had an ovarian cystectomy for a serous papillary cystadenoma, six inches in diameter, when ten weeks pregnant. The pregnancy was undisturbed. For the second patient, who was twelve weeks pregnant, operation was planned, but while she was at the toilet early on the morning of the operation, the parovarian cyst, five inches in diameter, was suddenly strangulated by the twisting of its pedicle. In that case the ovary had to be sacrificed as it was part of the strangulated mass. The pregnancy continued. The third patient, symptomless when six weeks pregnant, had three dermoid cysts enucleated, both ovaries being left entire. The largest cyst, six inches in diameter, was in the left ovary; it had one and a half turns in its pedicle without interference with its blood supply

and lay on the right side of the abdomen. The two smaller cysts were in the right ovary. The pregnancy was undisturbed. Dr. Meares said that the last two patients demonstrated the frequency of torsion, and the necessity for both early diagnosis and early surgical treatment, not only to prevent abortion, which followed torsion, but in order that the ovaries could be saved by performing cystectomy instead of having to resort to oophorectomy.

Dr. Meares also exhibited specimens and slides of a thecoma of the ovary with resultant hyperplasia of the endometrium, which had caused post-menopausal bleeding in a woman aged fifty-three years.

Modern Clinical Implications of the Rh Factor.

Dr. F. Bellingham discussed the Rh factor and its implications. In considering the serology of Rh-positive and Rh-negative groups he pointed out that each chromosome carried the Rh factor. One gene came from the father and one from the mother. For example, an Rh-positive parent might have D and D, making him homozygous, or D and d, making him heterozygous. If the chromosome carried d and d, then the individual was said to be Rh-negative. Anti-D was the commonest Rh antibody encountered. Discussing the ways in which iso-immunization to the Rh factor occurred, Dr. Bellingham said that, unlike anti-A and anti-B agglutinins, Rh agglutinins never occurred spontaneously. They resulted from either repeated blood transfusions or pregnancy, including abortions.

Dr. Bellingham then went on to consider the differential diagnosis of hæmolytic disease of the fœtus. He referred first of all to *hydrops fœtalis* and non-hydropic stillbirths, and pointed out that examination of cord blood in the former condition showed anæmia, hyperbilirubinæmia and erythroblastæmia; the last-mentioned condition might rarely be syphilitic or associated with congenital heart disease. With regard to *icterus gravis neonatorum* and congenital anæmia in the newborn, he mentioned three points: that physiological jaundice was due to physiological immaturity of the liver; that in Rh babies the rate of fall of hæmoglobin concentration was very rapid and a value of less than 14 grammes *per centum* was abnormal; that in normal babies nucleated red cells amounted to less than 5% and disappeared in one to two days, but erythroblastæmia might be present if the mother was diabetic. Other conditions to be considered were congenital obliteration of the bile duct, congenital syphilis, acute severe sepsis, and familial and acholuric jaundice; in relation to the last-mentioned condition, erythrocytes should be tested for their fragility. Finally hæmorrhagic disease of the newborn had to be borne in mind; in that condition there was hypoprothrombinæmia, and as a rule it had nothing to do with iso-immunization or hæmolysis; treatment was by the administration of vitamin *K* and the intravenous or intramuscular injection of adult blood or plasma. Dr. Bellingham said that serological tests were the most satisfactory for diagnosis. The most simple and reliable of those was the anti-human-globulin test ("Coombs"), which was simply a demonstration that the infant's erythrocytes were "coated" with immune anti-Rh antibody.

Dr. Bellingham then considered treatment. He said that there were only three lines of action to be considered: (i) the induction of abortion, which was very rarely necessary; (ii) the induction of premature labour (or Cæsarean section) about the thirty-seventh week, or the thirty-fifth week if the prognosis was bad; and (iii) the allowing of the pregnancy to go to term. He considered that all Rh-negative women should be tested for antibodies twice as a routine during the pregnancy. In relation to the treatment of the affected infant, valuable tests were (*a*) the anti-human-globulin test performed with cord blood, (*b*) hæmoglobin estimation, (*c*) estimation of the bilirubin content of the blood, and (*d*) examination of a blood film. The onset of jaundice was the most reliable clinical sign, and in all except mild cases the infant needed immediate transfusion. Exchange transfusion was better because it removed most of the Rh-positive erythrocytes, the time for replacement with Rh-negative erythrocytes was shorter, and it also removed a certain amount of Rh antibody. Breast feeding was allowed. The prognosis might be considered from the immediate and the long-term aspects. If the fœtus was born alive there was a two-to-one chance of its surviving the neonatal period. From the long-term viewpoint serious sequelæ of erythroblastosis might occur as a result of kernicterus developing in about 12% of cases; that meant neurological complications with various degrees of spasticity or mental retardation. When advice was given to parents of affected children regarding possible future pregnancies, it needed to be explained that the interval between pregnancies made no difference, the possibility of a normal baby depending on whether the father was homozygous or heterozygous (DD or Dd); the greater the number of normal offspring before the first affected one, the better was the prognosis. Reliance could not be placed on the antibody titre, except when it was higher than 1:500 in the early weeks of pregnancy.

(To be continued.)

Correspondence.

A MISSIONARY DOCTOR WANTED FOR THE NEW HEBRIDES.

Sir: Our Mission maintains a twenty-four bed hospital on the island of Iririki in Vila Harbour, New Hebrides. It serves both the European and native community of many islands within the group. Out-patients number between 3000 and 4000 per year.

The Missionary Medical Superintendent will be returning to Australia for furlough covering a period of approximately nine months commencing from the second half of October, 1949. The Board urgently requires the services of a doctor to fill the vacancy during furlough, and would welcome inquiries, particularly from such as are communicant members of a Protestant church.

The work involves general hospital practice, limited major surgery and some teaching of native trainees. The hospital is electrically equipped including a portable X-ray apparatus. An excellent opportunity is afforded a young doctor to obtain experience in tropical diseases and travel.

Free furnished quarters, passages, local transport, and freight on personal goods from Sydney are provided. If required, board is available in the missionary staff dining room at nominal cost. The salary is paid on a missionary fellowship basis and will be approximately at the rate of £450 *per annum*.

Inquiries may be made to the Australian Presbyterian Board of Missions, Box 100, G.P.O., Sydney. 'Phones: BX 2748 and WM 1908.

Yours, etc.,

V. W. Coombes,
General Secretary.

Australian Presbyterian Board of Missions,
Margaret Street,
Sydney.
September 22, 1949.

SELF-HELP INSURANCE FOR DOCTORS.

Sir: Notwithstanding the drubbing which Mr. Chifley and his advisers have meted out to a personal income earning group, the profession still continues to live in the mid-Victorian era. It treats each other, attached wives and children and all relatives *gratis*, as the old school tie insists on dog not eating dog. It also includes in the family the nursing profession, the hospital lay staff, the clergy, artists, sometimes the local politician, and various other poor but intelligent groups. Every member of the profession from junior to senior willingly makes this contribution to our struggling and over-taxed citizens, colleagues and supporters.

Apart from all the free work it is called upon to do by tradition, why should the profession continue to render this free service to its own members when such financially sound and excellent self-help organizations exist as the Metropolitan Hospitals Contribution Fund and the Medical Benefits Fund of New South Wales.

For under ten pounds *per annum*, the fees charged by these self-help organizations, the 7000 doctors in Australia could ensure that their personal bills to each other were paid without hardship to their colleagues, and in the course of normal practice be hundreds of pounds better off at the end of each financial year, as for every service they personally received and paid for they would get the fees from ten of their colleagues or dependants which they now treat as "L.O.G." It goes without saying that the profession would take nothing from their colleagues or dependants over and above what the insurance funds normally allotted for the particular service rendered.

Before encouraging the general public to avail themselves of these unique self-help organizations the profession should take in their own washing and give themselves some advantage from what a hard-earned art has initiated.

The public have been quick to realize the advantages. Why should the profession not avail itself of the cheapest form of security which has yet been created and that by

their own efforts? How often do we find the sick doctor himself worried about his hospital accounts, notwithstanding that he will have nothing to pay for the professional services of his colleagues?

The whole of the profession of Australia should immediately insure themselves in these two self-help organizations. For the ten pounds it will cost them they will receive twenty times that amount in the course of their normal interprofessional practice, and this holds for juniors as well as seniors.

As far seeing as the Americans are, their Blue Cross and the Blue Shield have never thought of the enormous advantages of insuring themselves in their own organizations. It is a ten to one investment, and the simplest way of implanting it is for the British Medical Association to require an intending member to be insured before election. It would be doing no more than most of the Hospitals Boards endeavour to do in regard to the Hospitals Contribution Fund when it comes to employing their nursing and lay staffs.

Let every doctor, young or old, turn up his appointment book and add up the number of *gratis* professional patients. He will not require a mathematical training to see what the odds are for his ten pounds' annual expenditure on self-help medical insurance.

Yours, etc.,

HERBERT SCHLINK.

Sydney,
September 27, 1949.

AIR TRAVEL AND MEDICAL FITNESS.

SIR: In your issue of September 3, Dr. E. H. Anderson drew attention to certain points arising out of your timely leading article of July 23.

I think it would be worth while to reemphasize that it should not be assumed without inquiry that oxygen (or pressurization) is available on any particular air transport service.

Your article stated "on flights of the first kind (to Britain, America and other far-off countries) pressurized planes fitted with oxygen are used. . . ." In fact, on overseas flights unpressurized as well as pressurized aircraft are used. On the pressurized aircraft on Australian overseas services, emergency oxygen is fitted for crew use only, so that in the event of pressure failure hypoxia in passengers can only be avoided by rapid loss of height to below 10,000 feet.

As regards domestic services, passenger oxygen equipment is standard on DC-4's, but even portable equipment is practically never routinely carried on smaller aircraft. On some services, oxygen might not be available even if asked for. If oxygen is likely to be needed for an intending passenger, the only safe procedure is to make a specific inquiry as to its availability from the airline concerned.

At present there is no official limit to the height at which unpressurized aircraft may fly; though flights over 10,000 feet are not common, nor are they especially rare.

Yours, etc.,

J. C. LANE,
Superintendent of Aviation Medicine.

Department of Civil Aviation,
522-536 Little Collins Street,
Melbourne, C.1.
September 23, 1949.

Obituary.

ARTHUR GRAHAM BUTLER.

THE following appreciation has been received from Dr. W. E. L. H. Crowther.

The death of Colonel A. Graham Butler, Medical Historian to the first Australian Imperial Force, was not known to me until noticed in the recent number of THE MEDICAL JOURNAL OF AUSTRALIA.

The appreciations by Mr. Victor Hurley and Dr. Alan S. Walker were so adequate that at this late date I hesitate to offer my own memories of a long and happy association with him.

When the Seventh Field Ambulance with which I was serving landed at Gallipoli, Butler already had a legendary fame and was the best known of the medical officers of the First Division. It was not until the spring of 1917, however, that our paths crossed. At this time, as a section commander of the Fourteenth Field Ambulance, I was responsible for part of the relief of his unit, the third, at that time at the advanced dressing station, on the Hindenburg Line in front of Bullecourt. Colonel Hearne, our Assistant Director of Medical Services (later killed on the ridge at Passchendaele), went forward with him that afternoon to look over the bearer posts and lines of evacuation. Vickers, my bearer sergeant, who was with them, commented on his return on their complete disregard of the heavy shelling in the Norieul Valley, and how, after the explosion of a salvo, they moved up to the shellholes to settle their argument as to the calibre of the guns employed, regardless of where the next group would land.

When in the following September the Division moved up for the Polygon Wood phase of the Passchendaele offensive, it was again his command, from which we took over the advanced dressing station and evacuation. On inquiring for him at their Menin Gate Headquarters, I was told he was up the line and had been since the previous afternoon. Later I found him, red eyed from dust and traces of gas, with his battered wide-brimmed hat down over his face. It was attached by a piece of thick string to the shoulder strap of his old tunic from which also hung his steel helmet and respirator. He was very cheerful and interested and had had a good night in some shelter he had found. Like his friend and co-historian, Dr. C. E. W. Bean, he had innumerable friends among our divisions, and whenever it could be done he was forward with the bearers rather than enduring the routine administrative work of even an advanced dressing station. My memory is that soon after the close of this offensive he was with Corps Headquarters for a period before his appointment to Administrative Headquarters, Horseferry Road. It was against all his inclination and wishes to leave the units with which he had worked since their formation; his consolation was that the collation of medical records required a return to the front at frequent intervals. He spent hours with unit commanders, all young and keen, of an average age of thirty, instructing how he wished our war diaries and records to be compiled and urging that all data concerned with training and operations should be sent to him. As a result sketches, diagrams, local maps and so on were impressed to make the records more complete. Realizing his distress at the meagre and scanty records of the work of the unit at Anzac, those who had served with it at that period combined to partially fill in the gaps. We looked forward always to his visits and he returned refreshed to his duties in London.

With the return to Australia came the long weary task of compiling the history. It was my custom when on an occasional visit to Melbourne to call at his office at Victoria Barracks. Discussing the progress of his work, he always spoke of his dread that his history would not be worthy of the men whose work he was recording. Indeed his quest for perfection greatly hampered him in his task. I still remember my pride in being asked to give in detail the scheme of evacuation of my bearers between certain critical dates. Our talk would continue with a walk across the Domain to the Gardens with lunch under the trees watching the wildfowl—altogether "a day in the sun".

Butler came to Hobart a few years ago as a delegate to the conference of the Returned Soldiers, Sailors and Airmen's Imperial League of Australia and loved every minute of it—it is not necessary to say what his visit meant to his friends and colleagues.

The last two contacts were by letter. The one to say in his generous way that he had enjoyed something I had written to the journal and to send an inscribed copy of his book "The Digger". "A little thing of my own which you may have seen . . . it gave me fun to write it, and these days one picks up happiness when and how one can." The other was, as it were, a last handshake. He was having a spell, he said, before a couple of operations. "The first restful time I have had for years. . . . I have various eccentricities to make the events more interesting, a systolic B.P. of 200 and numerous extrasystoles, very unpleasant. So life is full of interest and shortly incident."

There we see the serene outlook and indomitable courage so characteristic of the man.

The Federal Council truly spoke for all his colleagues in inviting his acceptance of the gold medal of the association, and especially for those who realized how much of material success he had put away from himself in undertaking his commission as their historian. Such a man, generous to a fault in his recognition of the merit of others, makes no provision for the recording of his own.

It would be very fitting if a foreword of the life and accomplishments of Colonel A. Graham Butler were added to future editions of his Official History, even perhaps to the one now in preparation by Dr. A. S. Walker.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 67, of September 15, 1949.

NAVAL FORCES OF THE COMMONWEALTH.

Permanent Naval Forces of the Commonwealth (Sea-Going Forces).

Appointment.—Bertram Charles Morgan is appointed Surgeon Lieutenant (for short service), dated 1st October, 1948 (amending Executive Minute No. 78 of 16th December, 1948).

Citizen Naval Forces of the Commonwealth.

Royal Australian Naval Reserve.

Termination of Appointments.—The appointment of Peter Eric Blaubaum as Surgeon Lieutenant is terminated, dated 28th June, 1949. The appointments of Russell Geoffrey Cole and Keith Gadsden McCullough as Surgeon Lieutenants are terminated, dated 27th June, 1949. The appointment of John Northwood Story as Surgeon Lieutenant is terminated, dated 21st June, 1949.

AUSTRALIAN MILITARY FORCES.

Royal Australian Army Medical Corps.

NX200502 Captain (Temporary Lieutenant-Colonel) D. H. Sutton relinquishes command, 20th Field Ambulance, 13th April, 1949, relinquishes the temporary rank of Lieutenant-Colonel and is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (2nd Military District), 26th July, 1949.

The following officers relinquish the temporary rank of Major and are transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)): Captains (Temporary Majors) QX501694 L. R. L. Menogue (3rd Military District), 5th July, 1949, and NX506351 W. R. Vautin (2nd Military District), 29th June, 1949.

V147237 Major J. J. Hurley is placed upon the Retired List (3rd Military District) with permission to retain his rank and wear the prescribed uniform, 5th July, 1949.

To be Temporary Lieutenant-Colonel, 8th July, 1949.—NX506297 Captain (Temporary Major) J. Prior.

Citizen Military Forces.

Northern Command: First Military District.

Royal Australian Army Medical Corps (Medical).—The resignation of 1/39018 Captain (provisionally) H. L. J. Lusby of his commission is accepted, 22nd May, 1949. To be Temporary Major, 27th June, 1949: 1/21022 Captain H. Glynn-Connolly, M.C.

Eastern Command: Second Military District.

Royal Australian Army Medical Corps (Medical).—2/104175 Captain N. R. Scott-Young is appointed from the Reserve of Officers with regimental seniority in accordance with Army seniority, 1st May, 1948. To be Captain (provisionally), 3rd May, 1949: 2/111127 Robert Harvey Higham.

Southern Command: Third Military District.

Royal Australian Army Medical Corps (Medical).—3/63671 Major K. H. Heard is absorbed within a vacancy in the authorized establishment of Majors and receives pay and allowances of that rank, 1st June, 1949. The resignation of 3/58525 Captain (provisionally) K. Archer of his commission is accepted, 23rd March, 1949. The resignation of 3/101004 Captain (provisionally) B. Hudson of his commission is accepted, 21st May, 1949. To be Captain (provisionally), 15th July, 1949: 3/73277 John Willmott Bennett.

Western Command: Fifth Military District.

Royal Australian Army Medical Corps (Medical).—5/32057 Major R. G. Linton is appointed from the Reserve of Officers

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DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED SEPTEMBER 17, 1949.[1]

Disease.	New South Wales.	Victoria[4].	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.[2]	Australian Capital Territory.	Australia.[3]
Ankylostomiasis	*	9(9)	..	..	2	..	..	..	11
Anthrax	*	..	..	..	..	..	..	..	..
Beriberi	*	*	*	*	*	*	..	*	..
Bilharziasis	*	..	..	..	..	..	..	..	..
Cerebro-spinal Meningitis	3(2)	3	1(1)	..	..	..	..	..	7
Cholera	..	..	..	..	..	..	..	..	..
Coastal Fever(*a*)	*	*	..	*	*	*	*	*	..
Dengue	*	*	*	*	*	*	..	*	..
Diarrhœa (Infantile)	..	..	6(1)	..	..	..	..	..	..
Diphtheria	10(3)	..	2	..	1	1(1)	..	..	6
Dysentery(*b*)	*	8(7)	1(1)	..	2	..	..	2	14
Encephalitis Lethargica	..	..	..	..	..	..	..	..	13
Erysipelas	*	*	*	..	*	*	..	..	..
Filariasis	*	..	..	..	..	..	..	..	..
Helminthiasis	*	..	*	*	*	*	*	*	..
Hydatid	*	*	*	*	*	*	*	..	..
Influenza	*	*	*	..	*	*	..	*	..
Leprosy	..	..	..	..	4	..	..	..	4
Malaria(*c*)	*	(*c*)	2(1)(*c*)	(*c*)	(*c*)	(*c*)	(*c*)	(*c*)	2(*c*)
Measles	*	*	*	89(32)	*	*	..	..	89
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	2(1)	42(22)	..	16(15)	1(1)	4(2)	..	..	65
Psittacosis	*	..	*	..	*	*	*	*	..
Puerperal Fever	1(1)	..	..	..	..	..	..	..	1
Rubella	*	*	*	*	2	*	..	2	4
Scarlet Fever	25(17)	12(4)	10(7)	9(4)	..	6(2)	..	..	62
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	*	..	..	*	*	*	*	*	..
Trachoma	*	..	*	*	*	*	*	*	..
Tuberculosis(*d*)	21(18)	15(5)	12(6)	7(6)	11(6)	3	..	..	69
Typhoid Fever(*e*)	..	..	..	..	..	..	1	1	1
Typhus (Endemic)(*f*)	..	..	2(1)	..	..	..	..	..	2
Undulant Fever	*	*	..	..	..	..	*	..	..
Weil's Disease(*g*)	*	*	*	*	*	*	*	*	..
Whooping Cough	*	*	*	55(10)	*	*	..	..	55
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] The form of this table is taken from the *Official Year Book of the Commonwealth of Australia*, Number 36, 1944-1945. Figures in parentheses are those for the metropolitan area.
[2] Figures not available.
[3] Figures incomplete owing to absence of returns from Northern Territory.
* Not notifiable.
(*a*) Includes "Mossman" and "Sarina" fevers. (*b*) Includes amœbic and bacillary. (*c*) Statistics inexact with varying practice with regard to relapses in Service cases infected overseas. (*d*) Includes all forms except in New South Wales and Northern Territory, where only pulmonary tuberculosis is notifiable. (*e*) Includes enteric fever, paratyphoid fevers and other Salmonella infections. (*f*) Cases reported include scrub, murine and tick typhus. (*g*) Includes leptospiroses, Weil's and para-Weil's disease.

with regimental seniority in accordance with Army seniority, 1st May, 1948. 5/26392 Captain (Temporary Major) A. J. King relinquishes the temporary rank of Major and is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (5th Military District) with the honorary rank of Major, 23rd June, 1949. To be Captain (provisionally), 4th July, 1949: 5/26400 Mervyn Noel Orton.

Reserve Citizen Military Forces.

Royal Australian Army Medical Corps.

1st Military District: To be Honorary Captains.—Keith Archer, 24th March, 1949, and Henry Lindsay John Lusby, 23rd May, 1949. The notifications respecting Captains G. H. Ellis and O. W. Powell which appeared in Executive Minute No. 188 of 1947, promulgated in *Commonwealth Gazette* No. 241 of 1947, are withdrawn.

2nd Military District.—The resignation of Honorary Captain K. X. Croese of his commission is accepted, 21st June, 1949.

3rd Military District: To be Honorary Captain, 22nd May, 1949.—Bryan Hudson.

5th Military District: To be Honorary Major, 27th June, 1949.—Gordon Oxer.

Royal Australian Air Force.

Permanent Air Force: Medical Branch.

Stanley James Hill (277558) is appointed to a short-service commission on probation for a period of twelve months, 18th July, 1949, with the rank of Pilot Officer.

The date of acceptance of resignation of Flight Lieutenant B. S. Woods (297502) as approved in Executive Council Minute No. 29 of 1949, appearing in *Commonwealth of Australia Gazette* No. 49, dated 7th July, 1949 (page 1917), is amended to read 22nd July, 1949.

Bibliography of Scientific and Industrial Reports.

A CHANGE OF NAME.

The following statement has been received from the Information Service of the Commonwealth Scientific and Industrial Research Organization.

"Bibliography of Technical Reports" is the new title of the "Bibliography of Scientific and Industrial Reports", published monthly by the United States Department of Commerce (Office of Technical Services), and the following is an extract from the Director's letter to subscribers:

> We are trying to approach 100 per cent. abstracting because of the demand for this additional information—but the abstracts will be brief so as to maintain a reasonably large number of listings.
>
> The Bibliography will be shorter in length hereafter. Reflecting the desire of most of our readers, we are making efforts to carry simply the *best* reports rather than *all* the reports.
>
> You will find a new "Newsletter" section in the Bibliography. The Newsletter will also be available separately at 50 cents per year. This will contain "technical highlights" in the form of brief interpretive comments on selected O.T.S. reports as well as on technical information available from other sources.
>
> To widen the dissemination of O.T.S. material and in recognition of the shorter issue length, the Secretary of Commerce has approved *lower subscription rates.* In place of the present ten dollars per year, the Bibliography of Technical Reports will henceforth sell for *five dollars per year.*

We recently ceased publication of abstracts from this Bibliography and suggested that our readers consult it themselves at one of the reference libraries. The Commonwealth Scientific and Industrial Research Organization will continue to accept requests to procure specific reports, on a "cash-on-delivery" basis, from the United States. Requests should be addressed to the Officer-in-Charge, C.S.I.R.O. Information Service, 314 Albert Street, East Melbourne, C.2.

Medical Appointments.

Dr. L. C. Lum has been appointed Assistant Medical Superintendent (Medical), Royal Adelaide Hospital, Adelaide.

Dr. E. W. Abrahams has been appointed Director of Tuberculosis, Health and Medical Branch, Department of Health and Home Affairs, Queensland, in pursuance of the provisions of *The Public Service Acts,* 1922 *to* 1948, and *The Health Acts,* 1937 *to* 1948, of Queensland.

Diary for the Month.

Oct. 11.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
Oct. 11.—New South Wales Branch, B.M.A.: Organization and Science Committee.
Oct. 13.—Victorian Branch, B.M.A.: Organization Subcommittee.
Oct. 14.—Queensland Branch, B.M.A.: Council Meeting.
Oct. 17.—Victorian Branch, B.M.A.: Finance, House and Library Subcommittee.
Oct. 18.—New South Wales Branch, B.M.A.: Medical Politics Committee.
Oct. 19.—Western Australian Branch, B.M.A.: General Meeting.
Oct. 20.—New South Wales Branch, B.M.A.: Clinical Meeting.
Oct. 20.—Victorian Branch, B.M.A.: Executive Meeting.

Medical Appointments: Important Notice.

Medical practitioners are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135 Macquarie Street, Sydney): Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester United Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

Manuscripts forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to The Medical Journal of Australia alone, unless the contrary be stated.

All communications should be addressed to the Editor, The Medical Journal of Australia, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

Members and subscribers are requested to notify the Manager, The Medical Journal of Australia, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

Subscription Rates.—Medical students and others not receiving The Medical Journal of Australia in virtue of membership of the Branches of the British Medical Association in the Commonwealth can become subscribers to the journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £3 *per annum* within Australia and the British Commonwealth of Nations, and £4 10s. *per annum* within America and foreign countries, payable in advance.